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(54) Title: COMPOSITIONS AND METHODS TO PREVENT TOXICITY INDUCED BY NONSTEROIDAL ANTIINFLAMMATORY DRUGS

(57) Abstract

Nonsteroidal antiinflammatory drugs which have been substituted with a nitrogen monoxide group; compositions comprising: (i) a nonsteroidal antiinflammatory drug, which can optionally be substituted with a nitrogen monoxide group and (ii) a compound that directly donates, transfers or releases a nitrogen monoxide group (preferably as a charged species, particularly nitrosonium); and methods of treatment of inflammation, pain, gastrointestinal lesions and/or fever using the compositions are disclosed. The compounds and compositions protect against the gastrointestinal, renal and other toxicities that are otherwise induced by nonsteroidal antiinflammatory drugs.

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COMPOSITIONS AND METHODS TO PREVENT TOXICITY INDUCED BY NONSTEROIDAL ANTIINFLAMMATORY DRUGS

This application is a continuation-in-part of U.S. application serial no. 08/543,208 filed October 13, 1995, which is a continuation-in-part of U.S. application serial no. 08/425,090 filed April 19, 1995 (co-pending).

This invention relates to the field of "aspirin-like" or nonsteroidal antiinflammatory drug compounds and compositions that prevent, reduce or reverse the gastrointestinal, renal, and other toxicities associated with nonsteroidal antiinflammatory drugs.

Arena *et al.*, WO94/12463, discloses the chemistry and pharmacology of nitroxybutylester[$(CH2)_4$-ONO_2] derivatives of several aryl propionic acid non-steroidal antiinflammatory drugs including ketoprofen, flurbiprofen, suprofen, indobufen and etodolac. Studies on nitroxybutylester derivatives of flurbiprofen and ketoprofen are also reported in Wallace *et al.*, *Gastroenterology, 107*:173-179 (1994). See, also, Cuzzolin *et al.*, *Pharmacol. Res., 29(1)*:89-97 (1994); Reuter *et al.*, *Life Sci. (USA)*, 55/1(PL1-PL8) (1994); Reuter *et al.*, *Gastroenterology, 106(4)*:Suppl. A759 (1994); Wallace *et al.*, *Eur. J. Pharmacol., 257(3)*:249-255 (1994); Wallace *et al.*, *Gastroenterology, 106(4)*:Suppl. A208 (1994); and Conforti *et al.*, *Agents-Actions, 40(3-4)*:176-180 (1993). These publications uniformly examine and rely upon the use of indirectly linked nitrogen dioxide substitutions.

The present invention is based on the discovery by the inventors that it is possible to link a nitrogen monoxide group, nitric oxide (NO), to a non-steroidal antiinflammatory agent and that the resulting compounds not only possess potent analgesic/antiinflammatory properties but has a much reduced potential for producing gastrointestinal lesions (ulcers).

The present invention is further based on the discovery by the inventors that it is possible to coadminister a nonsteroidal antiinflammatory drug (NSAID) and a compound that directly donates, releases or transfers nitrogen monoxide(preferably as a charged species, particularly nitrosonium) to prevent, reduce, or reverse the gastrointestinal, renal, and other toxicities induced by the NSAID. NSAIDs are antiinflammatory, analgesic and antipyretic compounds that act as cyclooxygenase. the enzyme responsible for the biosyntheses of the prostaglandins and certain autocoids, inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2) and as inhibitors of both cyclooxygenase and lipoxygenase. A nitric oxide donor is a compound that contains a nitric oxide moiety and which directly releases or directly chemically transfers nitrogen monoxide (nitric oxide), preferably in its positively charged nitrosonium form, to another molecule. Nitric oxide donors include but are not limited to S-nitrosothiols, nitrites, N-oxo-N-nitrosamines, and substrates of various forms of nitric oxide synthase.

In one aspect the present invention provides a compound comprising a non-steroidal antiinflammatory agent to which is directly or indirectly linked at least one NO group. The non-steroidal antiinflammatory agent can, for example, be an aryl propionic acid or an enolic anilide. The invention also provides compositions comprising such compounds in a pharmaceutically acceptable carrier.

In another aspect the invention provides a composition comprising a mixture of a therapeutically effective amount of a nonsteroidal antiinflammatory agent and an

NSAID toxicity reducing amount of a compound that donates, transfers or releases nitric oxide.

In another aspect the present invention provides a composition comprising a non-steroidal antiinflammatory agent to which is directly or indirectly linked at least one NO group and a compound that donates, transfers or releases nitric oxide. The non-steroidal antiinflammatory agent can, for example, be an aryl propionic acid or an enolic anilide. The invention also provides compositions comprising such compounds in a pharmaceutically acceptable carrier.

In another aspect the invention provides a method for treating inflammation, pain and/or fever in an individual in need thereof which comprises administering to the individual a nonsteroidal antiinflammatory agent, which may optionally be substituted with at least one NO group, and a compound that donates, transfers or releases nitric oxide. The NSAID or NSAID directly or indirectly linked to at least one NO group, and nitric oxide donor can be administered separately or as components of the same composition.

In another aspect the invention provides a method of treating inflammation, pain and/or fever in an individual in need thereof which comprises administering to the individual a composition comprising a therapeutically effective amount of an NSAID, which may optionally be substituted with at least one NO group, and an NSAID toxicity reducing amount of a nitric oxide donor in a pharmaceutically acceptable carrier. Such compositions are discussed in more detail below.

In another aspect the invention provides a method to decrease or reverse the gastrointestinal toxicity of nonsteroidal antiinflammatory drugs administered to an animal, particularly a human, by co-administering to said animal a nitric oxide donor. The NSAID and nitric oxide donor can be administered separately or as components of the same composition.

In another aspect the invention provides a method to decrease or reverse the renal toxicity of nonsteroidal antiinflammatory drugs administered to an animal, particularly a human, by co-administering to said animal a nitric oxide donor. The NSAID and nitric oxide donor can be administered separately or as components of the same composition.

In another aspect the invention provides a method to accelerate gastrointestinal tissue repair in an animal, particularly a human, by administering to said animal a nitric oxide donor. The NSAID and nitric oxide donor can be administered separately or as components of the same composition.

The compounds and compositions of the present invention are novel and can be utilized to treat numerous inflammatory disease states and disorders. For example, reperfusion injury to an ischemic organ, *e.g.*, reperfusion injury to the ischemic myocardium, myocardial infarction, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, hypertension, psoriasis, organ transplant rejections, organ preservation, impotence, radiation-induced injury, asthma, atherosclerosis, thrombosis, platelet aggregation, metastasis, influenza, stroke, burns, trauma, acute pancreatitis, pyelonephritis, hepatitis, autoimmune diseases, insulin-dependent diabetes mellitus, disseminated intravascular coagulation, fatty embolism, Alzheimer's disease, adult and infantile respiratory diseases, carcinogenesis and hemorrhages in neonates.

The NSAID can be nitrosylated through sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation), carbon and nitrogen.

The term "lower alkyl" herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like.

The term "alkoxy" herein refers to RO-wherein R is lower alkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like.

The term "alkoxyalkyl" herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like.

The term "alkenyl" herein refers to a branched or straight chain C_2-C_{10} hydrocarbon which also comprises one or more carbon-carbon double bonds.

The term "nitrite" herein refers to -O-NO.

The term "amino" herein refers to $-NH_2$.

The term "nitrosothiol" herein refers to -S-NO.

The term "cyano" herein refers to -CN.

The term "hydroxy" herein refers to -OH.

The term "thionitrate" herein refers to $-S-NO_2$.

The term "alkylsulfinyl" herein refers to R_{30}-$S(O)_2$- wherein R_{30} is a branched or unbranched lower alkyl of up to four carbons.

The term "carboxamido" herein refers to $-C(O)NH_2$.

The term "carbamoyl" herein refers to $-O-C(O)NH_2$.

The term "carboxyl" herein refers to $-CO_2H$.

The term "alkylamino" herein refers to $R_{31}NH$-wherein R_{31} is a lower alkyl group, for example, methylamino, ethylamino, butylamino, and the like.

The term "dialkylamino" herein refers to $R_{32}R_{33}N$- wherein R_{32} and R_{33} are independently selected from lower alkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like.

The term "N-alkylcarbamoyl" herein refers to $-O-C(O)N(R_{31})(H)$ wherein R_{31} is as previously defined.

The term "N,N-dialkylcarbamoyl" herein refers to $-O-C(O)N(R_{32})(R_{33})$ wherein R_{32} and R_{33} are as previously defined.

The term "nitroso" herein refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

The term "nitro" herein refers to the group $-NO_2$ and "nitrosated" refers to compounds that have been substituted therewith.

The term "aryl" herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, and nitro. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkyl" herein refers to a lower alkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like.

The term "arylthio" herein refers to $R_{54}S$- wherein R_{54} is an aryl group.

The term "cycloalkyl" herein refers to an alicyclic group comprising from 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "bridged cycloalkyl" herein refers to two or more cycloalkyl radicals fused via adjacent or non-adjacent carbon atoms, including but not limited to adamantyl and decahydronapthyl.

The terms " halogen" or "halo" herein refer to I, Br, Cl or F. The term "haloalkyl" herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The term "heteroaryl" herein refers to a mono- or bi-cyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring. Heteroaryl groups (including bicyclic heteroaryl groups) can be unsubstituted or substituted with one, two, or three substituents independently selected from lower alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo and nitro. Examples of heteroaryl groups include but are not limited to pyridine, pyrazine, pyrimidine, pyridazine, pyrazole, triazole, thiazole, isothiazole, benzothiazole, benzoxazole, thiadiazole, oxazole, pyrrole, imidazole, and isoxazole.

The term "heterocyclic ring" herein refers to any 3-, 4-, 5-, 6-, or 7-membered nonaromatic ring containing at least one nitrogen atom which is bonded to an atom which is not part of the heterocyclic ring. In addition, the heterocyclic ring may also contain a one additional heteroatom which may be nitrogen, oxygen, or sulfur.

The term "heterocyclic compounds" herein refers to mono and polycyclic compounds containing at least one heteroaryl or heterocyclic ring.

Compounds of the invention which have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. It is to be understood that the present invention anticipates and includes within its scope all such isomers and mixtures thereof.

The NSAID used in the compositions of the invention can be any of those known to the art, including those exemplified below.

First, despite the introduction of many new drugs, aspirin (acetylsalicylic acid) is still the most widely prescribed antiinflammatory, analgesic and antipyretic agent and is a standard for the comparison and evaluation of all other NSAIDs. Salicylic acid itself is so irritating that it can only be used externally. However, derivatives, particularly salicylate esters and salts, have been prepared which provide ingestible forms of the salicylates which have the desired antiinflammatory and other properties. In addition to aspirin which is the acetate ester of salicylic acid, are the diflurophenyl derivative (diflunisal) and salicylsalicylic acid (salsalate). Also available are the salts of salicylic acid, principally sodium salicylate. Sodium salicylate and aspirin are the two most commonly used preparations for systemic treatment. Other salicylates include salicylamide, sodium thiosalicylate, choline salicylate and magnesium salicylate. Also available are combinations of choline and magnesium salicylates.

Also contemplated are 5-aminosalicylic acid (mesalamine), salicylazosulfapyridine (sulfasalazine) and methylsalicylate.

Another group of NSAID drugs included are the pyrazolon derivatives. Included in this group are, for example, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone (azapropazone).

Another group of such NSAIDs are the para-aminophenol derivatives. These are the so-called "coal tar" analgesics and include phenacetin and its active metabolite acetaminophen.

Another group of compounds contemplated include indomethacin, a methylated indole derivative, and the structurally related compound, sulindac.

Also contemplated is a group of compounds referred to as the fenamates which are derivatives of N-phenylanthranilic acid. The most well known of these compounds are mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids. They are used either as the acid or as pharmaceutically acceptable salts.

Another contemplated NSAID is tolmetin which, like the other NSAIDs discussed herein, causes gastric erosion and prolonged bleeding time.

Another group of NSAID compounds are the propionic acid derivatives. Principal members of this group are ibuprofen, naproxen, flurbiprofen, fenoprofen and ketoprofen. Other members of this group, in use or study in countries outside the U.S.: include fenbufen, pirprofen, oxaprozin, indoprofen and tiaprofenic acid.

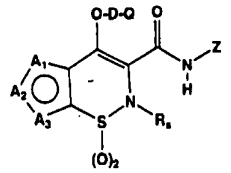
Also contemplated are piroxicam and amperoxicam, oxicam derivatives which are a class of antiinflammatory enolic acids. The other related compounds tenoxicam and tenidap are also contemplated. Another compound that is particularly

and tenidap are also contemplated. Another compound that is particularly contemplated is diclophenac, one of the series of phenylacetic acid derivatives that have been developed as antiinflammatory agents. Other NSAIDs which are contemplated as suitable in the compositions of the invention include etodolac and nabumentone.

Each of the above contemplated NSAIDs is described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (8th Edition), McGraw-Hill, 1993, Pgs. 638-381.

The compositions of the invention can also include NSAIDs which have been nitrosylated through sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation), carbon and nitrogen, including those specifically discussed below and in the working examples that follow.

One embodiment of this aspect includes nitroso substituted compounds of the formula:



I

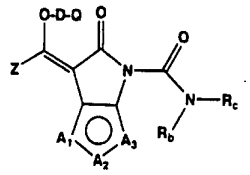
wherein

D is selected from (i) a covalent bond; (ii) $-C(R_a)-O-C(O)-Y-[C(R_b)(R_c)]_p-T$ in which R_a is lower alkyl, cycloalkyl, aryl or heteroaryl, Y is oxygen, sulfur, or NR_i in which R_i is hydrogen or lower alkyl, R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, aminoarylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6 and T is a covalent bond, oxygen, sulfur, or nitrogen and Q is -NO or $-NO_2$ with the proviso that -T-Q is not $-O-NO_2$; or (iii)$-(CO)-T_1-[C(R_b)(R_c)]_p-T_2$

wherein T_1 and T_2 are independently selected from T, and wherein R_b, R_c, p and T are as defined above and with the provision that -T-Q does not equal -O-NO_2; Z is an aryl or heteroaryl; and

A_1, A_2 and A_3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring and each is independently selected from (1) C-R_i wherein R_i at each occurrence is independently selected from hydrogen, lower alkyl, lower haloalkyl, alkoxyalkyl, halogen or nitro; (2) N-R_d wherein R_d at each occurrence is independently selected from a covalent bond to an adjacent ring atom in order to render the ring aromatic, hydrogen, lower alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; (3) sulfur; (4) oxygen; and (5) B_a=B_b wherein B_a and B_b are each independently selected from nitrogen or C-R_i wherein at each occurrence R_i is as defined above.

Another embodiment of this aspect is nitroso substituted compounds of the formula:

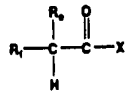


II

wherein

R_b, R_c, D, Q, Z, A_1, A_2 and A_3 are defined as above.

Another embodiment is compounds of the formula:



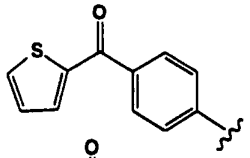
III

wherein

R_e is hydrogen or lower alkyl;

R_f is selected from

(1)



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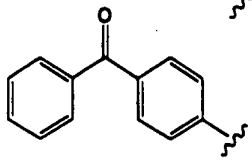

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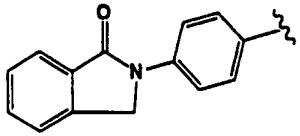

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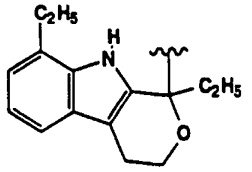

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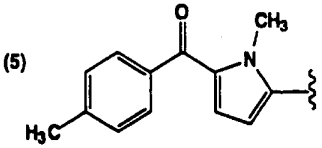

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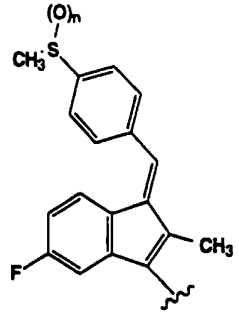

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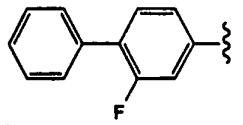

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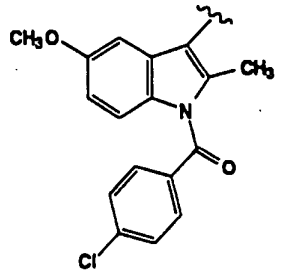
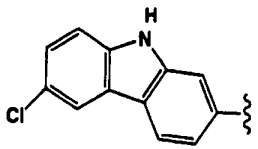
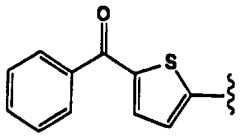
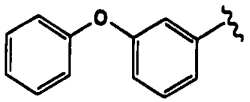
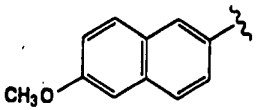
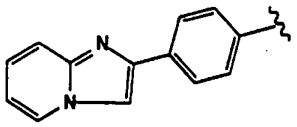


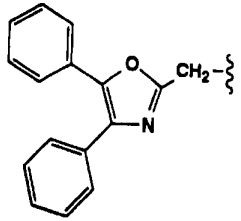
(9) 

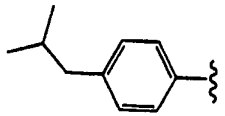
(10) 

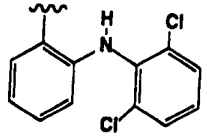
(11) 

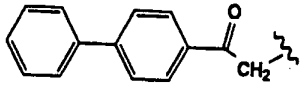
(12) 

(13) 

(14) 

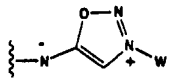
(15) 

(16) 

(17) 

in which n is 0 or 1; and

X is (1) -Y-[C(R_b)(R_c)]p_1-G-[C(R_b)(R_c)]p_2-T-Q, wherein G is (i) a covalent bond; (ii) -T-C(O)-; (iii) -C(O)-T; (iv) -C(Y-C(O)-R_m)- wherein R_m is heteroaryl or heterocyclic ring; p_1 and p_2 are independently selected from p and in which Y, R_b, R_c, p and T are as defined above with the proviso that -T-Q is not -O-NO_2; (2)



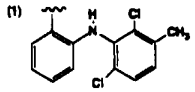
in which W is a heterocyclic ring or NR_hR_i wherein R_h and R_i are independently selected from lower alkyl, aryl or alkenyl; (3) -Y_1[C(R_b)(R_c)]$_t$-Z-[C(O)-Y_2-[C(R_b)(R_c)]$_{p1}$-T-Q]$_{p2}$ wherein Y_1, and Y_2 are independently selected from Y, S is an integer from 0 to 3, and R_b, R_c, Z, T, and Q are as defined above with the proviso that -T-Q is not is -O-NO_2.

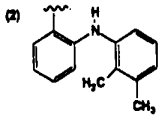
Another embodiment of this aspect is compounds of the formula:

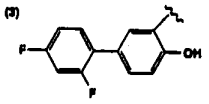
 XV

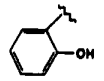
wherein

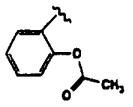
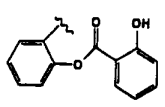
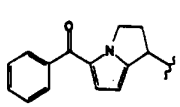
R_g is selected from

(1) 

(2) 

(3) 

(4) 

(5)  (6)  (7) 

and X is defined as above.

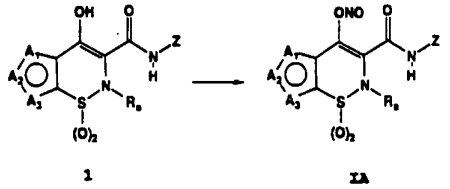
The present invention also relates to processes for preparing the compounds of formula (I), (II), (III) or (IV) and to the intermediates useful in such processes.

Compounds of the present invention may be synthesized as shown in reaction Schemes I through XI presented below, in which R_a, R_b, R_c, R_d, R_e, R_f, R_g, A_1, A_2, A_3, p, and Z are as defined above or as depicted in the reaction schemes for formulas I, II, III or IV; P^1 is an oxygen protecting group and P^2 is a sulfur protecting group. The reactions are performed in solvents appropriate to the reagents and materials employed are suitable for the transformations being effected. It is understood by those skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to skilled practitioners in the art. The use of sulfur and oxygen protecting groups is well known in the art for protecting thiol, alcohol, and amino groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, *c.f.*, T.H. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1991).

Nitroso compounds of formula (I) wherein A_1, A_2, A_3, R_a, and Z are defined as above and an O-nitrosyated enol is represenatative of the D group as defined

above may be prepared according to reaction Scheme I. The enolic form of the β-keto amide of the formula 1 is reacted with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite [c.f., Hakimelahi et al., *Helvetica Chimica Acta*, *67*, 907 (1984)], or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, tetrahydrofuran (THF), dimethylforamide (DMF), or acetonitrile with or without am amine base such as pyridine or triethylamine to afford the O-nitrite IA.

Scheme I

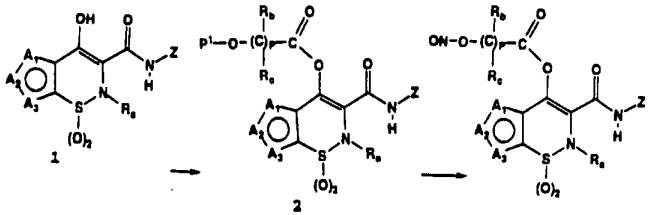


1 IA

Nitroso compounds of formula (I) wherein p, A_1, A_2, A_3, R_a, R_b, R_c, and Z are defined as above and an O-nitrosylated ester is representative of the D group as defined above may be prepared according to Scheme II. The enolic form of the β-keto amide of the formula 1 is converted to the ester of the formula 2 wherein p, R_b and R_c are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P^1 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane,

THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IB**.

Scheme II

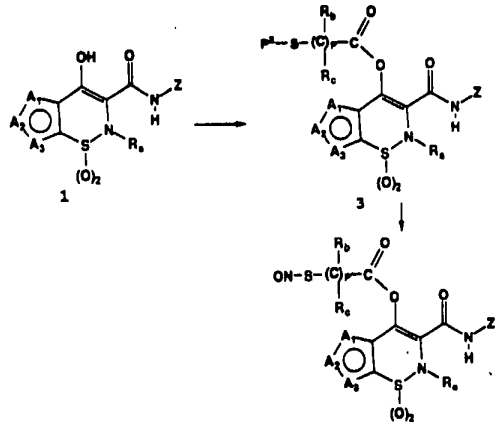


IB

Nitroso compounds of formula (I) wherein p, A_1, A_2, A_3, R_a, R_b, R_c, and Z are defined as above and an S-nitrosyated enol ester is representative of the D group as defined above may be prepared according to reaction Scheme III. The enolic form of the β-keto amide of the formula 1 is converted to the ester of the formula 3 wherein p, R_b, and R_c are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P^2 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base

is typically utilized to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methyene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IC. Alternatively, reacting this intermediate with a stoichiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula IC.

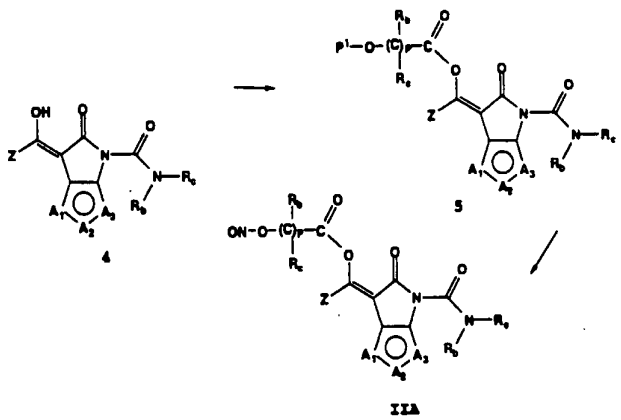
Scheme III



IC

Nitroso compounds of formula (II) wherein p, A_1, A_2, A_3, R_b and R_c, and Z are defined as above and an O-nitrosylated ester is representative of the D group as defined above may be prepared according to Scheme IV. The enolic form of the β-keto amide of the formula 4 is converted to the ester of the formula 5 wherein p, R_b and R_c are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P^1 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IIA.

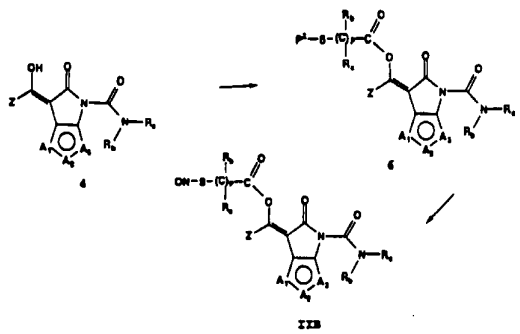
Scheme IV



Nitroso compounds of formula (II) wherein p, A_1, A_2, A_3, R_b, R_c, and Z are defined as above and an S-nitrosyated enol ester is represenatative of the D group as defined above may be prepared according to reaction Scheme V. The enolic form of the β-keto amide of the formula 4 is converted to the ester of the formula 6 wherein p, R_b and R_c are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P^2 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base

is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methyene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine acid affords the compound of the formula **IIB**. Alternatively, reacting this intermediate with a stiochiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula **IIB**.

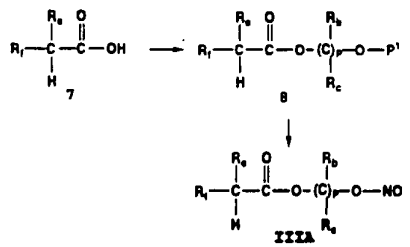
Scheme V



Nitroso compounds of formula (**III**) wherein p, R_b, R_c, R_e and R_f are defined as above and an O-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme VI. An acid of the formula **7** is converted into the ester of the formula **8** wherein p, R_b and R_c are defined as above by reaction with an appropriate monoprotected diol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of **7** with a chloroformate

such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as dichloromethane, diethylether, or THF. The mixed anhydride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine. Alternatively, the acid **7** may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine and a tertiary amine base such as triethyl amine to afford the ester **8**. Alternatively, the acid **7** and monoprotected diol may be coupled to afford **8** by treatment with a dehydration agent such as 1,3-dicyclohexylcarbodiimide (DCC). Alternatively, compound **7** may be first converted into an alkali metal salt such as the sodium, potassium, or lithium salt, and reacted with an alkyl halide which also contains a protected hydroxyl group in an polar solvent such as DMF to afford **8**. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IIIA**.

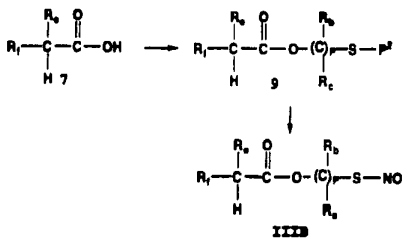
Scheme VI



Nitroso compounds of formula (III) wherein p, R_b, R_c, R_e, and R_f are defined as above and a S-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme VII. An acid of the formula 7 is converted into the ester of the formula 9 by reaction with an appropriate protected thiol containing alcohol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of 7 with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the thiol containing alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine. Alternatively, the acid 7 may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the monoprotected thiol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine and a tertiary amine base such as triethyl amine to afford the ester 9. Alternatively, the acid and thiol containing alcohol may be coupled to afford 9 by treatment with a dehydration agent such as DCC. Alternatively, compound 7 may be first converted into an alkali metal salt such as the sodium, potassium, or

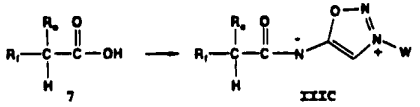
lithium salt, and reacted with an alkyl halide which also contains a protected thiol group in an polar solvent such as DMF to afford 9. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IIIB**. Alternatively, this intermediate may be reacted with a stoichiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula **IIIB**.

Scheme VII



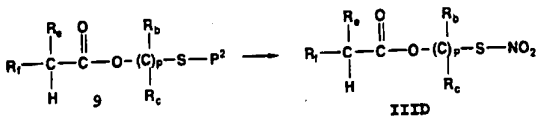
Nitroso compounds of formula (III) wherein W, R_c, and R_f are defined as above and a 6-W-substituted sydnonimine wherein W is as defined above is representative of the X group as defined above may be prepared according to Scheme VIII. An acid of the formula 7 is converted into the carboximide of the formula IIIC by reaction with a 6-W-substituted sydnonimine. Preferred methods for the preparation of carboximides are initially forming the mixed anhydride via reaction of 7 with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the 6-W-substituted sydnonimine to afford IIIC. Alternatively, the acid 7 may be coupled to the 6-W-substituted sydnonimine to afford IIIC by treatment with a dehydration agent such as DCC. Alternatively, the acid 7 may be converted into an active ester by reaction with a suitably substituted phenol utilizing any of the conditions for ester formation described for Scheme VI, followed by reaction with a 6-W-substituted sydnonimine. Preferred 6-W-substituted sydnonimines are 1,2,6,4-oxatriazolium, 6-amino-6-morpholine and 1,2,6,4-oxatriazolium, 6-amino-6-(6-chloro-2-methyl -benzene) and preferred active esters are para-nitrophenyl, 2,4,5-trichlorophenyl, and pentafluorophenyl.

Scheme VIII



Nitroso compounds of formula (III) wherein p, R_b, R_c, R_e, and R_f are defined as above and a S-nitrosated ester is representative of the X group as defined above may be prepared according to Scheme IX. The protected thiol containing ester of the formula 9 is deprotected. Zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group. Reaction of the thiol group(s) excess dinitrogen tetroxide in a solvent such as methylene chloride, THF, DMF, or acetonitrile affords the compound of the formula IIID.

Scheme IX

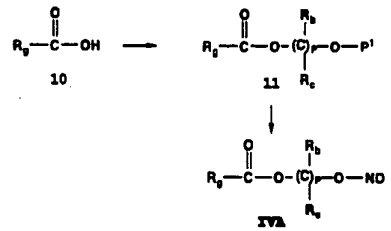


IIID

Nitroso compounds of formula (IV) wherein p, R_b, R_c, and R_g are defined as above and an O-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme IX. An acid of the formula **10** is converted into the ester of the formula **11** wherein p, R_b, and R_c are defined as above, by reaction with an appropriate monoprotected diol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of **10** with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine. Alternatively, the acid **10** may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine and a tertiary amine base such as triethylamine to afford the ester **11**. Alternatively, the acid **10** and monoprotected diol may be coupled to afford **11** by treatment with a dehydration agent such as DCC. Alternatively, compound **10** may be first converted into an alkali metal salt such as the sodium, potassium, or lithium salt, which is then reacted with an alkyl halide which also contains a protected hydroxyl group in an polar solvent

such as DMF to afford **11**. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethyl amine affords the compound of the formula **IVA**.

Scheme X

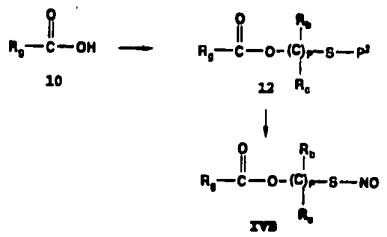


IVA

Nitroso compounds of formula (IV) wherein R_g is defined as above and a S-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme X. An acid of the formula **10** is converted into the ester of the formula **12** by reaction with an appropriate protected thiol containing alcohol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of **10** with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the

protected thiol containing alcohol preferably in the presence of a condensation catalyst such as 4-dimethylaminopyridine. Alternatively, the acid **10** may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the protected thiol containing alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamineo pyridine and a tertiary amine base such as triethyl amine to afford the ester **12**. Alternatively, the acid and protected thiol containing alcohol may be coupled to afford **12** by treatment with a dehydration agent such as DCC. Alternatively, compound **10** may be first converted into an alkali metal salt such as the sodium, potassium, or lithium salt, which is then reacted with an alkyl halide which also contains a protected thiol group in an polar solvent such as DMF to afford **12** . Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile affords the compound of the formula **IVB**. Alternatively, this intermediate may be reacted with a stoichiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula **IVB**

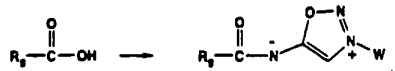
Scheme XI



Nitroso compounds of formula (**IV**) wherein R_8 is defined as above and a 6-substituted sydnonimine is representative of the X group as defined above may be prepared according to Scheme XI. An acid of the formula **10** is converted into the carboximide of the formula IVC by reaction with a 6-W-substituted sydnonimine wherein W is as defined above. Preferred methods for the preparation of carboximides are initially forming the mixed anhydride via reaction of **10** with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the 6-W-substituted sydnonimine to afford **IVC**. Alternatively, the acid **10** may be coupled to the 6-W-substituted sydnonimine afford **IVC** by treatment with a dehydration agent such as DCC. Alternatively, the acid **10** may be converted into an active ester by reaction with a suitably substituted phenol utilizing any of the conditions for ester formation described above, followed by reaction with a 6-W-substituted sydnonimine. Preferred 6-W-substituted sydnonimines are 1,2,6,4-oxatriazolium, 6-amino-6-morpholine and 1,2,6,4-

oxatriazolium, 6-amino-6-(6-chloro-2-methyl -benzene) and preferred active esters are para-nitrophenyl, 2,4,5-trichlorophenyl, and pentafluorophenyl.

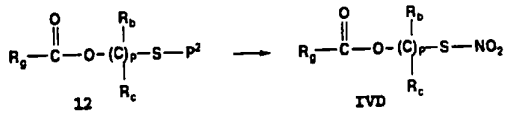
Scheme XII



10 IVC

Nitroso compounds of formula (IV) wherein p, R_b, R_c, and R_g are defined as above and a S-nitrosated ester is representative of the X group as defined above may be prepared according to Scheme XIII. The protected thiol containing ester of the formula 12 is deprotected. Zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group. Reaction of the thiol group(s) with excess dinitrogen tetroxide in a solvent such as methylene chloride, THF, DMF, or acetonitrile affords the compound of the formula IVD.

Scheme XIII



12 IVD

The compounds that donate, transfer or release nitric oxide can be any of those known to the art, including those mentioned and/or exemplified below.

Nitrogen monoxide can exist in three forms: NO^- (nitroxyl), NO• (nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical, because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to nitric oxide radical, nitrosonium and nitroxyl do not react with O_2 or O_2^-• species, and are also resistant to decomposition in the presence of redox metals. Consequently, administration of NO equivalents does not result in the generation of toxic by-products or the elimination of the active NO moiety.

Compounds contemplated for use in the invention are nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer nitric oxide to a site of its activity, such as on a cell membrane, *in vivo*. As used here, the term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitric oxide species, particularly including nitrosonium ion (NO^+) and nitroxyl ion (NO^-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitric oxide releasing, delivering or transferring compounds, having the structure F-NO_v, wherein F is a nitric oxide releasing, delivering or transferring moiety and v is an integer of 1 or 2, include any and all such compounds which provide nitric oxide

to its intended site of action in a form active for their intended purpose. As used here, the term "NO adducts" encompasses any of such nitric oxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, S-nitroso amino acids, S-nitroso-polypeptides, organic nitrites and organic thionitrates. It is contemplated that any or all of these "NO adducts" can be mono- or poly-nitrosylated and/or nitrosated at a variety of naturally susceptible or artificially provided binding sites for nitric oxide.

One group of such NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. Such compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars, S-nitrosylated-modified and unmodified oligonucleotides (preferably of at least 5, and more particularly 5-200, nucleotides); and an S-nitrosylated hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon, or an aromatic hydrocarbon; S-nitroso hydrocarbons having one or more substituent groups in addition to the S-nitroso group; and heterocyclic compounds. S-nitrosothiols and the methods for preparing them are described in U.S. Patent Application No. 07/943.834, filed September 14, 1992, Oae *et al.*, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983); Loscalzo *et al.*, *J. Pharmacol. Exp. Ther.*, *249*(3):726-729 (1989) and Kowaluk *et al.*, *J. Pharmacol. Exp. Ther.*, *256*:1256-1264 (1990), all of which are incorporated in their entirety by reference.

One particularly preferred embodiment of this aspect relates to S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. For example, such compounds include the following: S-nitroso-N-acetylcysteine, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine and S-nitroso-glutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur group on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator(TPA) and cathepsin B; transport proteins, such as lipoproteins, heme proteins such as hemoglobin and serum albumin; and biologically protective proteins, such as the immunoglobulins and the cytokines. Such nitrosylated proteins are described in PCT Publ. Applic. No. WO 93/09806, published May 27, 1993. Examples include polynitrosylated albumin where multiple thiol or other nucleophilic centers in the protein are modified.

Further examples of suitable S-nitrosothiols include those having the structures:

(i) $CH3[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20 and R_b and R_c are as defined above;

(ii) $HS[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20; and

(iii) $ONS[C(R_b)(R_c)]_xV$

wherein x equals 2 to 20 and V is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro and aryl; and x, R_b and R_c are as defined above.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which may be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. Alternatively, they may be

nitrosated by reaction with an organic nitrite such as tert-butyl nitrite, or an nitrosonium salt such as nitrosonium tetraflurorborate in an inert solvent.

Another group of such NO adducts are those wherein the compounds donate, transfer or release nitric oxide and are selected from the group consisting of compounds that include at least one ON-O-, ON-N- or ON-C- group. The compound that includes at least one ON-O-, ON-N- or ON-C- group is preferably selected from the group consisting of ON-O-,ON-N- or ON-C-polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O-, ON-N- or ON-C-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O-, ON-N- or ON-C-sugars; ON-O-, ON-N- or ON-C-modified and unmodified oligonucleotides (preferably of at least 5, and more particularly 5-200, nucleotides), ON-O-, ON-N- or ON-C-hydrocarbons which can be branched or unbranched, saturated or unsaturated aliphatic hydrocarbons or aromatic hydrocarbons; ON-O-, ON-N- or ON-C- hydrocarbons having one or more substituent groups in addition to the ON-O-, ON-N- or ON-C- group; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of such adducts are 2-hydroxy-2-nitrosohydrazines which donate, transfer or release nitric oxide and have a $R_{100}R_{200}$-N(O$^-$M$^+$)-NO group wherein R_{100} and R_{200} include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds. M$^+$ is a metal cation, such as, for example, a Group I metal cation.

Another group of such adducts are thionitrates which donate, transfer or release nitric oxide and have the structure R_{100}-(S)-NO_2 wherein R_{100} is as described

above for the N-oxo-N-nitrosoamines. Particularly preferred are those compounds where R_{100} is a polypeptide or hydrocarbon.

Agents which stimulate endogenous NO synthesis such as L-arginine, the substrate for nitric oxide synthase, are also suitable for use in accordance with the invention.

When administered *in vivo*, the compositions may be administered in combination with pharmaceutical carriers and in dosages described herein.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compounds may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Dosage forms for topical administration of the composition can include creams, sprays, lotions, gels, ointments and the like. In such dosage forms the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque lotions with, for example, benzyl alcohol 1% (wt/wt) as preservative,

emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution and polyethylene glycol 400. They can be mixed to form a white, smooth, homogeneous, opaque creams with, for example, benzyl alcohol 2% (wt/wt) as preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, and sorbitol solution. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g. gauge, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer, adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

Suppositories for rectal administration of the drug composition, such as for treating pediatric fever *etc.*, can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed an a solvent or suspending medium.

While the compositions of the invention can be administered as a mixture of an NSAID and a nitric oxide donor, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state that one is targeting for treatment.

The compositions of this invention can further include conventional excipients, *i. e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, *etc*. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc*.

Various delivery systems are known and can be used to administer a therapeutic compound or composition of the invention. *e.g.*, encapsulation in liposomes, microparticles, microcapsules and the like.

The therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include, but are not limited to, those formed with free amino groups such as those derived from hydrochloric, phosphoric, sulfuric, acetic, oxalic, tartaric acids, *etc.*, and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, *etc.*

The term "therapeutically effective amount," for the purposes of the invention, refers to the amount of the nitric oxide adduct which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges for effective amounts of each nitric oxide adduct is within the skill of the art. Generally, the dosage required to provide an effective amount of the composition, and which can be adjusted by one of ordinary skill in the art will vary, depending on the age, health, physical condition, sex, weight, extent of disease of the recipient, frequency of treatment and the nature and scope of the disorder.

The amount of a given NSAID which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Reference is again made to Goodman and Gilman, *supra*; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and to Drug Facts and Comparisons, Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances.

The amount of nitric oxide donor in a pharmaceutical composition may be in amounts of 0.1-10 times the molar equivalent of the NSAID. The usual daily doses of NSAIDs are 3-40 mg/kg body weight and the doses of nitric oxide donors in the pharmaceutical composition may be in amounts of 1-500 mg/kg body weight daily and more usually about 1-50 mg/kg. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, *supra*.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The following non-limitative examples further describe and enable one of ordinary skill in the art to make and use the invention. Flash chromatography was performed on 40 micron silica gel (Baker).

Example 1

Cholest-5-en-3β-O-nitroso alcohol

Cholesterol (0.242 g, 0.62 mmol) was dissolved in anhydrous methylene chloride (3 mL) and pyridine (0.103 g, 3.45 mmol) was added, followed by nitrosonium tetrafluoroborate (0.036 g, 0.31 mmol). After stirring for 1 hour at room temperature, an additional nitrosonium tetrafluoroborate (0.099 g, 0.85 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was purified by flash chromatography on silica gel, deactivated with

triethylamine, eluted methylene chloride to give 0.165 g (64 % yield) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.86 (d, 6 H), 0.92 (d. 3 H), 1.05-1.75 (m, 21 H), 1.80-2.01 (m, 6 H), 2.25-2.47 (m, 2 H), 5.23 (m. 1 H), 5 44 (m, 1 H).

Example 2

N-(N-L-γ-glutamyl- S-Nitroso-L-cysteinyl)glycine

N-(N-L-γ-glutamyl-L-cysteinyl)glycine (100 g, 0.325 mol) was dissolved in deoxygenated water (200 ml) and 2N HCl (162 ml) at room temperature and then the reaction mixture was cooled to 0 °C. With rapid stirring, a solution of sodium nitrite (24.4 g, 0.35 mol) in water (40 ml) was added and stirring with cooling of the reaction mixture was continued for approximately 1 hour after which time the pink precipitate which formed was collected by vacuum filtration. The filter cake was resuspended in chilled 40% acetone-water (600 ml) and collected by vacumm filtration. The filter cake was washed with acetone (2 X 200 ml) and ether (100 ml) and then dried under high vacuum at room temperature in the dark to afford the title compound as a pink powder. ^{1}H NMR (D_2O) δ:1.98 (m, 2 H), 2.32 (t,2 H), 3.67 (t, 1 H), 3.82 (s 2 H), 3.86 (dd, 1 H), 3.98 (dd, 1 H), 4.53 (m, 1H).

Example 3

S-Nitroso-triphenylmethanethiol

Triphenylmethyl mercaptan (0.050g, 0.18 mmol) was dissolved in anhydrous methylene chloride and cooled to 0°C. Tert-butyl nitrite (0.186 g, 1.80 mmol) was added and the resulting mixture was stirred at 0°C for 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 1 hour. The solvent and excess of tert-butyl nitrite were evaporated to give the title compound as a green solid (0.054 g, 98 %). ^{1}H NMR ($CDCl_3$) δ: 7.13-7.18 (m, 4 H), 7.25-7.39 (m, 11 H).

Example 4

4-O-Nitroso-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

4a. 4-Hydroxy-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

3-Benzoyl-α-methylbenzeneacetic acid (4 g, 16 mmol) and 100 μL DMF were dissolved in benzene (25 mL). Oxalyl chloride (1.6 mL, 18 mmol) was added dropwise. Stirring was continued for 2 hour before concentration to a syrup. Butanediol (9 mL, 100 mmol) and pyridine (1.67 mL, 21 mmol) were dissolved in methylene chloride (100 mL) and dioxane (15 mL) and cooled to 0°C. A solution of the acid chloride was added in methylene chloride (20 mL). The reaction mixture was stirred cold for 20 minutes then warmed to room temperature with stirring for 2 hour. The solution was washed 1 X 30 H_2O, 1 N HCl, satd $NaHCO_3$ and brine; dried over Na_2SO_4; and the volatiles were evaporated. The residue was filtered through a pad of silica gel eluting with 2:1 Hex:EtOAc to yield 4.8 g (91 %) of hydroxy ester. ^{1}H NMR ($CDCl_3$): d 7.41-7.81 (mult, 9 H), 4.08-4.15 (mult, 2 H), 3.79 (q, J = 7.2 Hz, 1 H), 3.59 (t, J = 6.3 Hz, 2 H), 1.53-1.69 (mult, 4 H), 1.53 (d, J = 7.2 Hz, 3H).

4b. 4-O-Nitroso-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

The product of Example 4a (1 g, 3.6 mmol) and pyridine (1.4 mL, 18 mmol) were dissolved in dichloromethane (15 mL) and cooled to -78°C. Nitrosonium tetrafluoroborate (840 mg, 7.2 mmol) was added and the solution was kept cold for 30 minutes. The reaction was warmed to room temperature with continued stirring for 1 hour. The mixture was diluted with dichloromethane and washed with 1N HCl, then brine. The solution was dried over sodium sulfate and evaporated. Chromatography on silica gel eluting with 9:1 Hexane:EtOAc gave 840 mg (76%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 7.41-7.80 (m, 9 H), 4.65 (m, 1 H), 4.11 (t, J = 6.0 Hz, 2 H), 3.79 (q, J = 7.2 Hz, 1 H), 1.65-1.72 (m, 4 H), 1.53 (d, J = 7.2 Hz, 3H). Anal Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 66.72; H, 5.95; N, 2.93

Example 5

4-O-Nitroso-4-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) pentyl ester

5a. 4-Hydroxy-4-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) pentyl ester

3-Benzoyl-α-methylbenzeneacetic acid (1.99 g, 7.7 mmol) in methylene chloride (20 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (1.36 mL, 15.7 mmol) and dimethylformamide (5 drops). A vigorous gas evolution was noted and the reaction mixture was stirred with slow warming and then overnight at ambient temperature. The volatile materials were removed *in vacuo* and the residue dissolved in methylene chloride (10 mL) and added dropwise to a precooled mixture of 2-methyl-2,5-pentanediol (3.7 g, 31 mmol) and pyridine (0.69 mL, 8.6 mmol) also in methylene chloride (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred under nitrogen with slow warming and then overnight at ambient temperature. The solution was washed successively with 2N hydrochloric acid and 2N sodium hydroxide, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:2). The product was isolated as an oil in 76% yield (2.1 g). ^{1}H NMR ($CDCl_3$) δ: 7.77-7.81 (m, 3 H), 7.64-7.43 (m, 6 H), 4.18-4.03 (m, 2 H), 3.80 (q, J=7.2 Hz, 1 H), 1.62-1.71 (m, 2 H), 1.54 (d, J=7.2 Hz, 3 H), 1.42-1.35 (m, 2 H), 1.16 (s, 6H). Anal calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.26; H, 7.43.

5b. 4-O-Nitroso-4-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) pentyl ester

A solution of the product of example 5a (0.4 g, 1.13 mmol) and pyridine (456 mL, 5.6 mmol) in methylene chloride (4 mL) was cooled to -78°C and nitrosonium tetrafluoroborate (262 mg,2.26 mmol) added. The reaction mixture was stirred at -78°C for 3 hours, washed with water and dried over sodium sulfate. After filtration and evaporation of the solvent the residual oil was subjected to column chromatography using ethyl acetate/hexane/triethylamine (18:80:2). The title compound was isolated as an oil

in 58% yield (0.25 g). ^{1}H NMR ($CDCl_3$) δ: 7.41-7.80 (m. 9 H). 4.02-4.17 (m. 2 H). 3.79 (q, J=7.2 Hz, 1 H), 1.73-1.79 (m. 2 H), 1.62-1.69 (m. 2 H). 1.52-1.55 (m. 9H).

Example 6

3-S-Nitroso-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

6a. 3-Mercapto-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

To 3-Benzoyl-α-methylbenzeneacetic acid (529 mg, 2 mmol) in benzene (5 mL) containing 5 ml of DMF was added oxalyl chloride (200 ml 2.2 mmol) dropwise. The reaction mixture was stirred 1.5 hour and then concentrated in vacuo to a syrup. The crude acid chloride was dissolved in dichloromethane (10 mL) and 3-mercapto-3-methyl butanol (Sweetman *et al. J. Med. Chem., 14*:868 (1971) (350 mg, 2.2 mmol) was added followed by pyridine (180 ml, 2.2 mmol). The reaction was stirred at room temperature for 1 hour and then it was diluted with dichloromethane and wash with 1N HCl, followed by saturated sodium bicarbonate, and then brine. The organic phase was dried over sodium sulfate, concentrated in vacuo, and the residue was chromatographed on silica gel eluting eith 9:1 hexane:ethyl acetate to afford 640 mg (90 %) of the product. ^{1}H NMR ($CDCl_3$) δ: 7.41-7.81 (m, 9 H), 4.28 (t, J = 7.1 Hz, 2 H), 3.78 (q, J = 7.2 Hz, 1 H), 1.88 (t, J = 7.0 Hz, 2 H), 1.69 (s, 1 H), 1.54 (d, J = 7.3 Hz, 3 H), 1.35 (s, 3 H), 1.34 (s, 3H).

6b. 3-S-Nitroso-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

To a solution of the product of Example 6a (105 mg, 0.3 mmol) in dichloromethane (4 mL) was added tert-butyl nitrite (70 mg, 0.6 mmol) in a dropwise fashion. The mixture was stirred at room temperature for 30 minutes. The solvent and excess reagent were evaporated to give 113 mg (quantitative) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 7.44-7.81 (m, 9 H), 4.29 (t, J = 6.9 Hz, 2 H), 3.77 (q, j = 7.2 Hz, 1 H), 2.51 (t, j = 6.9 Hz, 2 H), 1.841 (s, 3 H), 1.836 (s, 3 H), 1.53 (d, J = 7.2 3H).

Example 7

4-O-Nitroso-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

7a. (S)-6-methoxy-α-methyl-2-naphthaleneacetic acetyl chloride

Under a nitrogen atmosphere, oxalyl chloride (4.13 g, 30 mmol) was combined with methylene chloride (30 mL) and the resulting mixture was cooled to 0°C. Dimethylformamide (10 drops) was added and after 5 minutes of stirring, a suspension of (S)-6-methoxy-a-methyl-2-naphthaleneacetic acid (3.00 g, 13 mmol) in methylene chloride (30 mL) was added dropwise over a 30 minute period. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated in vacuo to give the product in a quantitative yield. ^{1}H NMR ($CDCl_3$) δ: 1.5 (d, 3 H), 3.91 (s, 1 H), 4.21 (q, 1 H), 7.09-7.14 (m, 1 H), 7.15 (d, 1 H), 7.42 (dd, 1 H), 7.68 (s, 2 H), 7.71 (s, 1H).

7b. 4-Hydroxy-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

Under a nitrogen atmosphere, 1,4-butanediol (5.30 mL, 60 mmol) and pyridine (0.95g, 12 mmol) were combined in methylene chloride (20 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the product of Example 7a (3.0 g, 12 mmol) in methylene chloride (15 ml) was added dropwise over 30 minute period. After stirring for 20 hours at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1 to 1:3) to afford 3.09 g (79% yield) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.47-1.68 (m, 4H, overlapping with a doublet at 1.57, 3 H), 3.55 (t, 2 H), 3.84 (q, 1 H), 3.91 (s, 3 H), 4.11 (t, 2 H), 7.11 (m, 2 H), 7.15 (d, 1 H), 7.42 (dd, 1 H), 7.67 (s, 1 H), 7.70 (d, 2 H).

7c. 4-O-Nitroso-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

The product of Example 7b (0.209 g. 0.69 mmol) was dissolved in anhydrous methylene chloride (4 mL) and pyridine (0.273 g, 3.45 mmol) was added. The resulting solution was cooled to -78°C and nitrosonium tetrafluoroborate (0.161 g. 1.38 mmol) was added in one portion. The reaction mixture was stirred for 1 hour at -78°C. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel , deactivated with triethylamine, eluted with ethyl acetate/hexane (1:2) to give 0.180 g (79% yield) of the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.58 (d, 3 H), 1.64-1.69 (m. 4 H), 3.85 (q, 1 H), 3.92 (s, 3 H), 4.11 (t, 2 H), 4.60 (s, 2 H), 7.10-7.13 (m, 1 H), 7.15 (d, 1 H), 7.39 (dd, 1 H), 7.66 (s, 1 H), 7.70 (d, 2 H).

Example 8

4-O-Nitroso-1-(1-)4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

8a. 4-Hydroxy-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

A stirred suspension of 1(4-chlorobenzoyl)5-methoxy-2-methylindoyl)-3-acetic acid (3.7 g, 10.5 mmol) in methylene chloride (20 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (1.8 mL, 20.6 mmol) and dimethylformamide (10 drops). A vigorous gas evolution was noted and the reaction mixture was stirred with gradual warming to room temperature and then at ambient for a total of 5 hours. The volatile materials were evaporated and the residue dissolved in dichloromethane (10 mL) and added dropwise to a precooled mixture 1,4-butanediol (4.7 g, 51.7 mmol) and pyridine (0.92 mL, 11.4 mmol) also in methylene chloride (10 mL). The reaction mixture was stirred with slow warming and then for 5 hours at ambient temperature under a nitrogen atmosphere. The solution was washed with 2N hydrochloric acid, saturated sodium bicarbonate, dried over anhydrous sodium sulfate,

filtered and concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:2). The product was isolated as an oil in 75% yield (3.3 g) which solidified on standing ^{1}H NMR ($CDCl_3$) δ: 7.67 (d, J=8.4 Hz, 2 H), 7.47 (d, J=8.5 Hz, 2 H), 6.97 (d, J=2.5 Hz, 1 H), 6.87 (d, J=9 Hz, 1 H), 6.67 (dd, J=2.5 Hz, 9Hz, 1 H), 4.13 (t, J=6.4 Hz, 2 H), 3.83 (s, 3 H), 3.66 (s, 2 H), 3.59 (t, J=6.4 Hz, 2 H), 2.38 (s, 3 H), 1.51-1.75 (m, 4H). Anal calcd for $C_{23}H_{24}ClNO_5$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.08; H, 5.60; N, 3.18.

8b. 4-O-Nitroso-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl- 1H-indole-3-acetic acid) butyl ester

A stirred solution of the product of Example 8a (1 g, 2.3 mmol), and pyridine (0.90 mL, 11.6 mmol) in methylene chloride (15 mL) at -78 ûC under a nitrogen atmosphere was treated with nitrosonium tetrafluoroborate (0.54 g, 4.6 mmol). The reaction mixture was stirred at -78 ûC for 3.5 hours, washed with water, dried with anhydrous sodium sulfate and the solvent removed *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:3). The product was isolated as a yellow oil in 69 % yield (0.73 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=8.5 Hz, 2Hz), 7.47 (d, J=8.5 Hz, 2 H), 6.95 (d, J=2.5 Hz, 1 H), 6.85 (d, J=5 Hz, 1 H), 6.66 (dd, J=2.5 Hz, 6.5 Hz, 1 H), 4.66 (br s, 2 H), 4.16 (t, J=6.6 Hz, 2 H), 3.83 (s, 3 H), 3.66 (s, 2 H), 2.39 (s, 3 H), 1.65-1.80 (m, 4H). Anal calcd for $C_{23}H_{23}ClN_2O_6$: C, 60.2; H, 5.05; N, 6.1. Found: C, 59.93; H, 4.87; N, 5.85.

Example 9

3-O-Nitroso-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

9a. 3-Hydroxy-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

A stirred suspension of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (5 g, 13.9 mmol) in methylene chloride (25 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (2.44 mL, 28 mmol) and dimethylformamide (10 drops). A vigorous gas evolution was noted and the reaction mixture was stirred with gradual warming for a total of 5 hours. The volatile materials were removed *in vacuo* and the residue dissolved in methylene chloride (15 mL) and added dropwise to a precooled mixture (+/-)-1,3-butanediol (8.83 g, 98 mmol) and pyridine (1.24 mL, 15.4 mmol) also in dichloromethane (10 mL). The reaction mixture was stirred with slow warming and then over the weekend at ambient temperature under a nitrogen atmosphere. The solution was washed with 2N hydrochloric acid, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:1). The product was isolated as an oil which solidified on standing in 75% yield (4.5 g). ^{1}H NMR indicated that the desired product was contaminated with an isomer and so it was recrystalised three times from diethyl ether/hexanes to give the desired product as a solid in 15 % yield (0.9 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=8.5 Hz, 2 H), 7.43 (d, J=8.5 Hz, 2 H), 6.95 (d, J=2.4 Hz, 1 H), 6.86 (d, J=9 Hz, 1 H), 6.67 (dd, J=9 Hz, 2.5 Hz), 4.30-4.39 (m, 1 H), 4.15-4.4 (m, 1 H), 3.83 (s, 3 H), 3.75-3.85 (m, 1 H), 3.67 (s, 2 H), 2.38 (s, 3 H), 1.95 (s, 1 H), 1.65-2.8 (m, 2 H), 1.16 (d, J=6.3 Hz, 3H). Anal calcd for $C_{23}H_{24}ClNO_5$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.29; H, 5.53; N, 3.18.

9b. 3-O-Nitroso-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

A stirred solution of the product of Example 9a (0.15 g, 0.34 mmol), and pyridine (0.14 mL, 1.7 mmol) in dichloromethane (2 mL) at -78°C under a nitrogen atmosphere was treated with nitrosonium tetrafluoroborate (0.08 g, 0.7 mmol). The reaction mixture was stirred at -78°C for 3.5 hours, washed with water, dried with anhydrous sodium sulfate and the solvent removed *in vacuo*. The residual oil was subjected to column

chromatography using ethyl acetate/hexane (1:3). The title compound was isolated as a yellow oil in 79 % yield (0.125 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=8.5 Hz, 2 H), 7.47 (d, J=8.5 Hz), 6.95 (d, J=2.3 Hz, 1 H), 6.86 (d, J=9 Hz, 1 H), 6.67 (dd, J=9 Hz, 2.5 Hz), 5.52 (sextet, J=6.5 Hz, 1 H), 4.06-4.24 (m, 2 H), 3.83 (s, 3 H), 3.65 (s, 2 H), 2.38 (s, 3 H), 2.05 (q, J=4 Hz, 2 H), 1.37 (d, J=6.5 Hz).

Example 10

4-O-Nitroso-4 methyl-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) pentyl ester

10a. 4-Hydroxy-4 methyl-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) pentyl ester

A stirred suspension of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (2.8 g, 7.7 mmol) in methylene chloride (25 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (1.36 mL, 15.7 mmol) and dimethylformamide (5 drops). A vigorous gas evolution was noted and the reaction mixture was stirred over ice for 30 minutes and then at room temperature for 3 hours. The volatile materials were removed *in vacuo* and the residue dissolved in methylene chloride (15 mL) and added dropwise to a precooled mixture of 2-methyl-2,5-pentanediol (3.7 g, 31 mmol) and pyridine (0.69 mL, 8.6 mmol) also in methylene chloride (10 mL). The reaction mixture was stirred under nitrogen with slow warming and then overnight at ambient temperature under a nitrogen atmosphere. The solution was washed with 2N hydrochloric acid, dried over anhydrous sodium sulfate, and filtered to give an oil which was concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:2) The product was isolated as an oil which solidified on standing in 100% yield (3.6 g). ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, J=8.9 Hz, 2 H), 7.47 (d, J=8.9 Hz, 2 H), 6.98 (d, J=2.5 Hz, 1 H), 6.87 (d, J=9 Hz, 1 H), 6.67 (dd, J=9 Hz, 2.5 Hz), 4.09-4.14 (m, 2 H), 3.83 (s, 3 H), 3.66 (s, 3 H), 2.39 (s, 3 H), 1.62-1.73 (m, 2

H), 1.37-1.43 (m, 2 H), 1.14 (s, 6H). Anal calcd for $C_{27}H_{32}ClNO_5$: C, 65.57; H, 6.16; N, 3.06. Found: C, 65.35; H, 6.25; N, 3.10.

10b. 4-O-Nitroso-4-methyl-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) pentyl ester

A solution the product of Example 10a (0.2 g, 0.44 mmol) and pyridine (176 mL, 2.2 mmol) in methylene chloride (2 mL) was cooled over dry ice and nitrosonium tetrafluoroborate (101 mg, 0.87 mmol) added. The reaction mixture was stirred at -78 ¡C for 3 hours, allowed to stand at the same temperature overnight, washed with water and dried over sodium sulfate. After filtration and evaporation of the solvent the residual oil was subjected to column chromatography (twice) using ethyl acetate/hexanes/triethylamine (25:73:2). The product was isolated as an oil in 42% yield (0.09 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=7.5 Hz, 2 H), 7.47 (d, J=7.5 Hz, 2 H), 6.96 (d, J=2.5 Hz, 1 H), 6.86 (d, J=9 Hz, 1 H), 6.66 (dd, J=7.5 Hz, 2.5 Hz), 4.11 (t, J=6Hz, 2 H), 3.83 (s, 3 H), 3.66 (s, 2 H), 2.39 (s, 3 H), 1.75-1.81 (m, 2 H), 1.64-1.72 (m, 2 H), 1.51 (s, 6H).

Example 11

3-S-Nitroso-3-methyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

11a. 3-Mercapto-3-methyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

A solution of α-methyl-4-(2-methylpropyl)benzeneacetic acid (1.52 g, 7.4 mmol) in methylene chloride (15 mL) cooled over ice and under nitrogen, was treated successively with oxalyl chloride (1.29 mL, 1.88 g, 14.8 mmol) and dimethylformamide (5 drops). The resultant solution was stirred over ice for 30 minutes and then at ambient temperature for 2 hours. The excess volatile materials were removed *in vacuo*

and the residue, dissolved in methylene chloride (5 mL), added to a precooled solution of pyridine (0.54 mL, 6.7 mmol) and 3-mercapto-3-methylbutanol (0.8 g, 6.7 mmol) in methylene chloride (15 mL). The reaction mixture was stirred over ice for 30 minutes and then at ambient temperature for 3 hours. The solution was then diluted with additional methylene chloride and washed with 2N hydrochloric acid, saturated sodium bicarbonate and brine and the organic phase dried with sodium sulfate, filtered and the solvent removed *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:3). The product was isolated as an oil in 68 % yield (1.4 g). ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, J=7.5 Hz, 2 H), 7.09 (d, J=7.5 Hz, 2 H), 4.25 (t, J=6.5 Hz, 2 H), 3.67 (q, J=7 Hz, 1 H), 2.44 (d, J=7.8 Hz, 2 H), 1.77-1.9 (m, 3 H), 1.48 (d, J=7 Hz, 3 H), 1.32 (s, 6 H), 0.89 (d, J=6.6 Hz, 6H).

11b. 3-S-Nitroso-3-methyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

A solution of the product of Example 11a (0.4 g, 1.2 mmol) in methylene chloride (8 mL) under nitrogen was treated with *tert* butyl nitrite (0.62 mL, 0.53 g, 5 mmol). After stirring for 1 hour at ambient temperature the volatile materials were evaporated. The residual green oil was subjected to column chromatography using ethyl acetate/hexanes (1:19). The product was isolated as a green oil in 65 % yield (0.25 g). ^{1}H NMR ($CDCl_3$) δ: 7.0 (d, J=7.5 Hz, 2 H), 7.10 (d, J=7.5 Hz, 2 H), 4.27 (t, J=6.9 Hz, 2 H), 3.66 (q, J=7.2 Hz, 1 H), 2.49 (t, J=6.6 Hz, 2 H), 2.44 (d, J=7.2 Hz, 2 H), 1.8-1.9 (m, 1 H), 1.81 (s, 3 H), 1.80 (s, 3 H), 1.48 (d, J=7.2 Hz, 3 H), 0.89 (d, J=6.6 Hz, 6H).

Example 12

4-O-Nitroso-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

12a. 4-Hyroxy-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

α-Methyl-4-(2-methylpropyl)benzeneacetic acid (4 g, 19 mmol) and 10 μL DMF were dissolved in benzene (30 mL). Oxalyl chloride was added dropwise. Stirring was continued for 2 hour before concentration to a syrup. Butanediol (9 mL, 100 mmol) and pyridine (1.67 mL, 21 mmol) were dissolved in dichloromethane (100 mL) and dioxane (15 mL) and cooled to 0°C. A solution of the acid chloride was added in dichloromethane (20 mL). The reaction mixture was stirred cold for 20 minutes then warmed to room temperature with stirring for 2 hour. The solution was washed H_2O, 1 N HCl, satd sodium bicarbonate and finally brine; dried over sodium sulfate; and evaporated. The residue was filtered through silica gel eluting with 2:1 hexane:EtOAc to yield 4.8 g (91 %) ofthe product. ^{1}H NMR ($CDCl_3$) δ: 7.19 (d, J = 6.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2H),4.07-4.12 (m, 2 H), 3.68 (q, J = 7.1 Hz, 1 H), 3.58 (t, J = 6.3 Hz, 1 H), 2.44 (d, J = 7.2 Hz, 2 H), 1.84 (sept, J = 6.8 Hz, 1 H), 1.50-1.69 (m, 4 H), 1.48 (d, J = 7.2 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 6H). Anal Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.17; H, 9.67

12b. 4-O-Nitroso-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

The product of Example 12a (1 g, 3.6 mmol) and pyridine (1.4 mL, 18 mmol) were dissolved in dichloromethane (15 mL) and cooled to -78°C. Nitrosonium tetrafluoroborate(840 mg, 7.2 mmol) was added and the solution was kept cold for 30 minutes. The reaction was warmed to room temperature with continued stirring for 1 hour. The mixture was diluted with dichloromethane and washed successively with 1N HCl, H_2O, and brine. The solution was dried over sodium sulfate and evaporated. Chromatography on silica gel eluting with 9:1 hexane:EtOAc gave 840 mg (76 %) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, J = 8.1 Hz, 2 H), 7.08 (d, J = 8.1 Hz, 2 H), 4.62 (m, 2 H), 4.07-4.12 (m, 2 H), 3.68 (q, J = 7.1 Hz, 1 H), 2.44 (d, J = 7.2 Hz, 2 H), 1.84 (sept, J = 6.7 Hz, 1 H), 1.64-1.68 (m, 4 H), 1.48 (d, J = 7.2 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 6H).

Example 13

4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) butyl ester

13a. 2-Fluoro-α-methyl-biphenylacetic acid chloride

Under a nitrogen atmosphere, oxalyl chloride (3.8 g, 30 mmol) was combined with methylene chloride (30 mL). The resulting mixture was cooled to 0°C and dimethylformamide (10 drops) was added. After 5 minutes of stirring a solution of 2-fluoro-α-methyl-biphenylacetic acid (3.0 g, 12 mmol) in methylene chloride (30 mL) was added dropwise,over a 30 minute period. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated to give the product in a quantitative yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ:1.58 (d, 3 H), 4.20 (q, 1 H), 7.11 (t, 2 H), 7.33-7.47 (m,Ê4 H), 7.54 (d, 2 H).

13b. 4-Hydroxy-1-(2-Fluoro-α-methyl-biphenylacetic acid) butyl ester

Under a nitrogen atmosphere, 1,4-butanediol (5.30 mL, 60 mmol) and pyridine (0.95Êg,Ê12 mmol) were combined in methylene chloride (20 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the product of Example 13a (3.0 g, 12 mmol) in methylene chloride (15 ml) was added dropwise over 30 minute period. After stirring for 20 hours at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica-gel eluting with methylene chloride/hexane (2:1) to give 1.66 g (44 %) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ:1.56 (d, 3 H), 1.61-1.77 (m, 4 H), 3.63 (t, 2 H), 3.75 (q,1 H), 4.14 (t, 2 H), 7.14 (t, 2 H), 7.27-7.45 (m, 4 H), 7.53 (d, 2 H).

13c. 4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) butyl ester

The product of Example 13b (0.190 g, 0.60 mmol) was dissolved in anhydrous methylene chloride (4 mL) and pyridine (0.237 g, 3.00 mmol) was added. The resulting solution was cooled to -78 ¡C and nitrosonium tetrafluoroborate (0.084 g, 0.72 mmol) was added. The reaction mixture was stirred for 1 hour at -78 ¡C and an additional nitrosonium tetrafluoroborate (0.047 g, 0.40 mmol) was added. After 30 minutes of stirring at -78 ¡C, the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel , deactivated with triethylamine, eluted with methylene chloride/hexane (3:1) to give 0.117 g (57 % yield) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 1.54 (d, 3 H), 1.68-1.83 (m, 4 H), 3.75 (q, 1 H), 4.14 (t, 2 H), 4.67 (s, 2 H), 7.14 (t, 2 H), 7.34-7.48 (m, 4 H), 7.54 (d, 2 H).

Example 14

4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) thiobutyl ester

14a. 1-tert-Butyldimethylsilyloxy-4-chloro-butanol

4-Chloro-1-butanol (5.43 g, 50 mmol) was dissolved in dimethylformamide (50ÊmL) and tert-butyldimethylsilylchloride (7.54 g, 50 mmol) was added, followed by imidazole (3.4 g, 50 mmol). After 24 hours of stirring at room temperature, the reaction mixture was diluted with hexane, washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated to give colorless liquid which was purified by chromatography on silica gel eluting with hexane/ethyl acetate (30:1) to give the product (7.26 g, 56 %). ^{1}H NMR ($CDCl_3$) δ: 0.05 (s, 6 H), 0.89 (s, 9 H), 1.64-1.68 (m, 2 H), 1.82-1.86 (m, 2 H), 3.57 (t, 2 H), 3.64 (t, 2 H).

14b. 4-tert-Butyldimethylsilyloxy-1-acetyl-thio-butyl ester

Under a nitrogen atmosphere, potassium thioacetate (0.53 g, 4.7 mmol) was dissolved in dimethylformamide (12 mL) and cooled to 0°C. A solution of the product of Example 14a (1.01 g, 3.91 mmol) in dimethylformamide (14 mL) was added. After 24 hours of stirring at room temperature, the solvent was evaporated and the residue was partioned between hexane and water (1:3). The organic layer was concentrated in vacuo to give the product (0.820 g, 71 %) as a yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6 H), 0.88 (s, 9 H), 1.57-1.64 (m, 4 H), 2.32 (s, 3 H), 2.89 (t, 2 H), 3.61 (t, 2 H).

14c. 4-tert-Butyldimethylsilyloxy-1-butane thiol

The product of Example 14b (5.7 g, 19.2 mmol) was dissolved in methanol (30 mL) and degassed with nitrogen gas for 30 minutes. Potassium carbonate (2.92 g, 21.1 mmol) was added in one portion at room temperature. After 1 hour of stirring at room temperature, the solvent was evaporated and the residue was partioned between hexane and water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give the product (3.2 g, 66 %). ^{1}H NMR ($CDCl_3$) δ: 0.05 (s, 6 H), 0.89 (s, 9 H), 1 34 (t, 1 H), 1.61-1.68 (m, 4 H), 2.51-2.57 (q, 2 H), 3.62 (t, 2 H).

14d. 4-tert-Butyldimethylsilyloxy-1-(2-Fluoro-α-methyl-biphenylacetic acid) thio-butyl ester

The product of Example 14c (1.37g, 5.4 mmol) was combined with pyridine (0.142Êg, 1.8 mmol) in methylene chloride (5 mL) and the resulting solution was cooled to 0 ¡C. A solution of the product of Example 13a (0.500 g, 1.8 mmol) in methylene chloride (4 mL) was added dropwise. After 22 hours of stirring at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated in

vacuo to give the product (0.526 g, 59 %). ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6 H), 0.89 (s, 9ÊH),1.56 (d, 3 H), 1.57-1.62 (m, 4 H), 1.88-2.29 (M, 2 H), 3.61 (t, 2 H), 7.15 (t,Ê2 H), 7.37-7.44 (m, 4 H), 7.54 (d, 2 H).

14e. 4-Hydroxy-1-(2-Fluoro-α-methyl-biphenylacetic acid) thio-butyl ester

The product of Example 14d (0.320 g, 0.64 mmol) was dissolved in the mixture of glacial acetic acid (0.5 mL), water (1 mL), and tetrahydrofuran (5 mL). The resulting solution was stirred for 24 hours at room temperature. The solvent was evaporated and the residue was partioned between methylene chloride and water. The organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to give the product (0.235 g, 100 %). ^{1}H NMR ($CDCl_3$) δ: 1.57 (d, 3 H), 1.58-1.69 (m, 4 H), 2.87 -2.93 (m, 2 H), 3.63 (t, 2 H), 3.84-3.92 (q, 1 H), 7.14 (t, 2 H), 7.37-7.44 (m, 4 H), 7.54 (d, 2 H).

14f. 4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) thio-butyl ester

The product of Example 14e (0.235 g, 0.61 mmol) was dissolved in anhydrous methylene chloride (3 mL) and pyridine (0.097 g, 1.23 mmol) was added. The resulting solution was cooled to -78°C and nitrosonium tetrafluoroborate (0.144 g, 1.23 mmol) was added in one portion. The reaction mixture was stirred for 1 hour at -78°C, the solvent was evaporated, and the residue was purified by chromatography on silica gel eluted with hexane/ethyl acetate (10:1) to give the title compound (0.110 g, 44 %). ^{1}H NMR ($CDCl_3$) δ: 157 (d, 3 H), 1.58-1.80 (m, 4 H), 3.85-3.93 (q, 1 H), 4.69 (t, 2 H), 7.14 (t, 2 H), 7.37-7.44 (m, 4 H), 7 55 (d, 2 H).

Example 15

4-O_Nitroso-2-methyl-N-2-pyridinyl-2-H-1,2-benzothiazine-2-carboxamide-1,1-dioxide

4-Hydroxy-2-methyl-N-2-pyridinyl-2-H-1,2-benzothiazine-2-carboxamide-1,1-dioxide (10.0 g, 30 mmol) was dissolved in anhydrous methylene chloride and cooled to 0 ¡C. Nitrosonium tetrafluoroborate (4.407 g, 38 mmol) was added in one portion, followed by pyridine (2.98 g, 38 mmol). The reaction mixture was stirred at room temperature for 7 days and then additional nitrosonium tetrafluoroborate (0.571 g, 1.72 mmol) was added. After stirring for 14 days at room temperature, the reaction mixture was poured into saturated sodium bicarbonate solution and extracted with methylene chloride. The solvent was evaporated, the residue was treated with ethyl acetate and filtered. The precipitate was dissolved in the mixture of methylene chloride/ ethyl acetate (1:1), and the solution was treated with decolorizing charcoal, filtered and concentrated in vacuo to give the title compound as a solid (1.56 g, 14 %). ^{1}HÊNMR ($CDCl_3$, 300 MHz), δ_2.96 (s, 3 H), 6.84 (t, 1 H), 7.17 (t, 1 H), 7.60-7.86 (m, 5 H), 8.22 (d, 1 H).

Example 16

4-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

16a. 3-benzoyl-α-methylbenzeneacetic acid chloride

3-Benzoyl-α-methylbenzeneacetic acid (3.2 g, 12.6 mmol) was treated in the same manner as set forth in Example 13a. Evaporation of the solvent, affored the the product as a yellow oil in a quantitative yield. ^{1}H NMR ($CDCl_3$), δ1.64 (d, 3 H), 4.21 (q, 1 H), 7.45-7.51 (m, 4 H), 7.62 (d, 1 H), 7 72-7.82 (m, 4 H).

16b. 4-Hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

Under a nitrogen atmosphere, 1,4-benzenedimethanol (0.507 g, 3.67 mmol) and pyridine (0.145 g, 1.83 mmol) were combined in methylene chloride (5 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the product of Example 16a (0.500 g, 1.83 mmol) in methylene chloride (5 mL) was added dropwise over 15 minutes. The reaction mixture was allowed to warm to room temperature and was then stirred over 2 days period. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with 1N hydrochloric acid and saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica-gel eluting with hexane/ethyl acetate (5:1 to 2:1) to give 0.092 g (42 %) of the product. ^{1}H NMR ($CDCl_3$) δ:1.60 (d, 3 H), 2.19 (s, 1 H), 3.90 (q, 1 H), 4.71 (s, 2 H), 5.17 (s, 2 H), 7.32 (dd, 4 H), 7 45-7.82 (m, 7 H), 7 84 (d, 2 H).

16c. 4-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

The product of Example 16b (0.090 g, 0.24 mmol) was treated in the same manner as set forth in Example 7c. Purification of the crude product was accomplished using flash chromatography on silica gel eluted with hexane/ethyl acetate (1:2) to give 0.069 g (71 %) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 300ÊMHz). δ1.55 (d, 3 H), 3.85 (q, 1 H), 5.11 (s, 2 H), 5.67 (s, 2 H), 7.27-7.80 (m, 9 H).

Example 17

3-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

17a. 3-Hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

Under a nitrogen atmosphere, 1,3-benzenedimethanol (0.500 g, 3.62 mmol) and pyridine (0.193 g, 2.44 mmol) were combined in methylene chloride (7 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the the product of Example 16a (0.665 g, 2.44 mmol) in methylene chloride (5 mL) was added dropwise over 15 minutes. The reaction mixture was stirred 2 hour 30 minutes at 0°C, concentrated in vacuo, diluted with ethyl acetate, washed with 1N hydrochloric acid and saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to give 0.530 g (58 %) of the product. ^{1}H NMR ($CDCl_3$) δ:1.55 (d, 3 H), 3.85 (q, 1 H), 4.64 (s, 2 H), 5.12 (d, 2 H), 7.13-7.18 (m, 1 H), 7.22 (s, 1 H), 7.26-7.30 (m, 2 H), 7.40-7.67 (m, 6 H), 7 73-7.78 (m, 3 H).

17b. 3-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

The product of Example 17a (0.74 g, 0.198 mmol) was treated in the same manner as set forth in Example 7c. Purification of the crude product was accomplished using flash chromatography on silica gel eluted with hexane/ethyl acetate (2:1) to give 0.046 g (71 %) of the title compound. ^{1}HÊNMR ($CDCl_3$) δ:1.55 (d, 3 H), 3.85 (q, 1 H), 5.12 (s, 2 H), 5.65 (s, 2 H), 7.18-7.31 (m, 4 H), 7.40-7.75 (m, 6 H), 7.76-7.79 (m, 3 H).

Example 18

3-O-Nitroso-hydroxymethylene-1-(1-(3-benzoyl-α-methylbenzeneacetic acid))-hydroxymethyladamantyl ester

18a. 1,3-Dicarboxymethyl adamantane

1,3-adamantanedicarboxylic acid (1.5 g, 5.95 mmol) was dissolved in methanol (30mL) and concentrated sulfuric acid (0.5 mL, 8.90 mmol) was added. The reaction

mixture was stirred at room temperature 20 hours. After concentration in vacuo, the residue was dissolved in methylene chloride, washed with water/brine (1:1), and dried over anhydrous sodium sulfate. The solvent was evaporated to give the product as a white solid in a quantitative yield. ^{1}H NMR ($CDCl_3$) δ:1.65-1.71 (m, 2 H), 1.76-1.82 (m, 8 H), 1.98-2.03 (m, 2ÊH), 2.07-2.18 (m, 2 H), 3.66 (s, 6 H).

18b. 1,3-Dihydroxymethyl adamantane

Under a nitrogen atmosphere, the product of Example 18a (1.33 g, 5.95 mmol) was dissolved in tetrahydrofuran (20 mL) and lithium aluminum hydride (0.316 g, 8.33 mmol) was added in one portion. The reaction mixture was allowed to reflux for 30 minutes, and was then quenched with water (0.316 mL, 8.33 mmol), 15 % sodium hydroxide solution (0.316 mL), and water (0.95 mL). After 15 hours of stirring at room temperature, the reaction mixture was filtered through PTFE and filtrate was partitioned between ethyl acetate and brine. The organic phase was dried over anhydrous sodium sulfate, filtered through PTFE and concentrated in vacuo to give the product (0.370 g, 28 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ:1.24-1.29 (m, 2 H), 1.42-1.52 (m, 8 H), 1.61-1.68 (m, 2 H), 2.07-2.16 (m, 2 H), 3.25 (s, 4 H).

18c. 3-Hydroxymethylene-1-(1-(3-benzoyl-α-methylbenzeneacetic acid))-hydroxymethyladamantyl ester

The product of Example 18b (0.199 g,0.54 mmol) was dissolved in tetrahydrofuran (10 mL) and pyridine (0.047 g, 0.59 mmol) was added. A solution of the product of Example 16a (0.161 g, 0.59 mmol) in chloroform (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 40 hours. The solvent was evaporated, the residue was dissolved in methylene chloride, washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (2:1) to give the

product (0.102 g, 28 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ:1.13-1.17 (m, 2 H), 1.18-1.55 (m, 10 H), 1.98-2.02 (m, 2 H), 3.18 (s, 2 H), 3.66 (d, 1 H), 3.77 (d, 1 H), 3.83 (q, 1 H), 7.43-7.68 (m, 6 H), 7.76-7.81 (m, 3 H).

18d. 3-O-Nitroso-hydroxymethylene-1-(1-(3-benzoyl-α-methylbenzeneacetic acid))-hydroxymethyladamantyl ester

The product of Example 18c (0.056 g, 0.083 mmol) was dissolved in anhydrous methylene chloride (2 mL) and pyridine (2 drops) was added. The resulting solution was cooled to -78°C and nitrosonium tetrafluoroborate was added in one portion. The reaction mixture was stirred for 3 hours at -78°C, washed with water, brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel eluted with hexane/ethyl acetate (15:1) to give the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ:1.15-1.19 (m, 2 H), 1.29-1.61 (m, 10 H), 1.98-2.03 (m, 2 H), 3.65 (d, 1 H), 3.77 (d, 1 H), 3.82 (q, 1 H), 4.33 (s, 2 H), 7.43-7.68 (m, 6 H), 7.76-7.81 (m, 3 H).

Example 19

3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) propyl ester hydrochloride

19a. 2-Mercapto-2-methyl-1-(2-tert-butyloxycarbamoyl-3-hydroxy-propionic acid) propyl amide

2-tert-Butyloxycarbamoyl-3-hydroxy-propionic acid (5 g, 24 mmol), 1-amino-2-methyl-2-propanethiol-HCl (3.5 g, 25 mmol), triethylamine (3.4 mL, 25 mmol), and 4-dimethylaminopyridine (300 mg, 2.4 mmol) were dissolved in methylene chloride (120 mL). DCC (5.1 g, 24 mmol) was added and the reaction mixture was stirred at room temperature overnight. The precipitate which formed was removed by filtration and washed with Et_2O. The mixed solvents were allowed to stand and more solid precipitated. This was removed by filtration and the mother liquor was

evaporated to leave 7.3 g of syrup. ^{1}H-NMR (DMSO-d_6): δ 7.78 (t, J = 5.6 Hz, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 4.82 (br s, 1 H), 3.96 (mult, 1 H), 3.54 (mult, 2 H), 3.32 (mult, 1H, obscured by H2O), 2.73 (dd, J = 5.6 and 13.3 Hz, 1 H), 1.37 (s, 9 H), 1.22 (s, 3 H), 1.20 (s, 3H). Anal calcd for $C_{12}H_{24}N_2O_4S$: C, 49.29; H, 8.27; N, 9.58; S, 10.96. Found: C, 49.39; H, 8.01; N, 9.44; S, 10.96.

19b. 3-(2-Mercapto-2-methyl propionic acid propyl amide)-2-tert-butyloxycarbamoyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) propyl ester

1-α-methyl-4-(2-methylpropyl)benzeneacetic acid (1.4 g, 6.8 mmol) and 10 μL of DMF were slurried in benzene (10 mL). Oxalyl chloride (630 μL, 7.2 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1 hour. The volatiles were removed on a rotary evaporator and the residue was reconcentrated from 5 mL of benzene. The reisdue was taken up in methylene chloride (10 mL) and cooled to 0°C. To this solution was added the product of Example 19a (2 g, 6.8 mmol) and pyridine (570 uL, 6.8 mmol) in methylene chloride (14 mL). The reaction was kept cold for 15 minutes then allowed to warm to room temperature. After 1 hour the mixture was diluted with methylene chloride and washed (1 X 10 ml) with 0.3 N HCl and satd $NaHCO_3$. The solvent was dried over Na_2SO_4 and evoporated in vacuo to leave 3.04 g of product as a mixture of inseparable diastereomers. ^{1}H-NMR ($CDCl_3$) δ: 7.15-7.18 (mult, 2 H), 7.07-7.14 (mult, 2 H), 6.57 (mult, 1 H), 5.24 and 5.04 (br s, 1 H), 4.48 (dd, J = 4.3 and 10.6 Hz, 1 H), 4.44 (dd, J = 5.0 and 10.6 Hz, 1 H), 4.28 (dd, J = 5.0 and 11.5 Hz, 1 H), 4.25 (mult, 1 H), 3.71 (q, J = 7.2 Hz, 1 H), 3.69 (q, J = 7.2 Hz, 1 H), 3.32 (dd, J = 6.7 and 13.6 Hz, 1 H), 3.21-3.24 (mult, 1 H), 3.17 (dd, J = 5.4 and 12.7 Hz, 1 H), 2.43 and 2.41 (d, J = 7.1 Hz, 2 H), 1.84 (sept, J = 6.7 Hz, 1 H), 1.46 and 1.47 (d, J = 7.1 Hz, 3 H), 1.43 (s, 9 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 0.88 (d, J = 6.6 Hz, 6H). Anal calcd for $C_{23}H_{40}N_2O_5S$: C, 62.47; H, 8.39; N, 5.83; S, 6.67. Found: C, 62.78; H, 8.30; N, 5.69; S, 6.31.

19c. 3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) propyl ester hydrochloride

The product of Example 19b (630 mg, 1.3 mmol) and tert-butyl nitrite (190 uL, 1.6 mmol) were dissolved in methylene chloride (8 mL) and stirred at room temperature for 1.5 hour. The solvent was evaporated and the residue was filtered through silica gel to give 430 mg of nitrosothiol. The amine protecting group was removed by stirring in 3N HCl in EtOAc (6 mL) for 1 hour. The solvent was removed to give 360 mg (62 % overall) of nitrosothiol hydrochloride (mixture of diastereomers) as a green solid. ^{1}H-NMR ($CDCl_3$) δ : 8.94-9.00 (mult, 1 H), 8.49 (br s, 3 H), 7.04-7.18 (mult, 4 H), 4.40-4.47 (mult, 1 H), 4.13 (mult, 2 H), 3.94-4.01 (mult, 1 H), 3.71-3.77 (mult, 2 H), 2.39/2.37 (d, J = 6.0 Hz, 2 H), 1.83/1.80/1.78/1.73 (s, 6 H), 1.36 (d, J = 6.0 Hz, 3 H), 0.83 (d, J = 6.4 Hz, 6H).

Example 20

3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(3-benzoyl-α-methylbenzeneacetic acid) propyl ester hydrochloride

20a. 3-(2-Mercapto-2-methyl propionic acid propyl amide)-2-tert-butyloxycarbamoyl-1-(3-benzoyl-α-methylbenzeneacetic acid) propyl ester

3-Benzoyl-α-methylbenzeneacetic acid (1.75 g, 6.8 mmol) and 10 uL of DMF were slurried in benzene (10 mL). Oxalyl chloride (630 uL, 7.2 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1 hour. The volatiles were removed on a rotary evaporator and the residue was reconcentrated from 5 mL of benzene. The reisdue was taken up in methylene chloride (10 mL) and cooled to 0 °C. To this solution was added the product of Example 19a (2 g, 6.8 mmol) and pyridine (570 uL, 6.8 mmol) in methylene chloride (14 mL). The reaction was kept cold for 15 minutes then allowed to warm to room temperature. After 1 hour the mixture was diluted with methylene chloride and washed (1 X 10) with 0.3 N HCl and satd $NaHCO_3$. The solvent was dried over Na_2SO_4 and removed on a rotary evaporator to leave 3.4 g of product.

Chromatography on silica gel eluting with 2:1 Hex:EtOAc gave 1.89 g (53%) of an inseparable mixture of diastereomers. ^{1}H-NMR ($CDCl_3$) δ:7.77-7.82 (mult, 3 H), 7.55-7.67 (mult, 2 H), 7.41-7.52 (mult, 4 H), 6.72-6.77 (mult, 1 H), 5.24 and 5.01 (br s, 1 H), 4.26-4.55 (mult, 3 H), 3.83 (q, J = 7.2 Hz, 1 H), 3.14-3.78 (mult, 2 H), 1.42 and 1.41 (s, 9 H), 1.32, 1.30, and 1.28 (s, 6H). Anal calcd for $C_{28}H_{36}N_2O_6S$: C, 63.61; H, 6.86; N, 5.30; S, 6.06. Found: C, 63.80; H, 6.76; N, 5.10; S, 5.88.

20b. 3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(3-benzoyl-α-methylbenzeneacetic acid) propyl ester hydrochloride

The product of Example 20a (520 mg, 1.0 mmol) and tert-butyl nitrite (140 μL, 1.2 mmol) were dissolved in methylene chloride (8 mL) and stirred at rooom temperature for 1.5 hour. The solvent was evaporated and the residue was filtered through a plug of silica gel to give 350 mg of nitrosothiol. The amine protecting group was removed by stirring in 3N HCl in EtOAc (6 mL) for 1 hour. The solvent was evaporated to give 290 mg (58 % overall) of the title compound (mixture of diastereomers) as a green solid. ^{1}H-NMR ($CDCl_3$) δ:8.94-9.01 (mult, 1 H), 8.47 (3 H), 7.48-7.73 (mult, 9 H), 4.39-4.47 (mult, 1 H), 4.16 (mult, 2 H), 3.89-4.06 (mult, 2 H), 3.69-3.77 (mult, 1 H), 1.89/1.81/1.79/1/70 (s, 6 H), 1.43/1.42 (d, J = 7.1 Hz, 3H).

Example 21

3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) propyl ester hydrochloride

21a. 3-(2-Mercapto-2-methyl propionic acid propyl amide)-2-tert-butyloxycarbamoyl-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) propyl ester

(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (1.75 g, 7.6 mmol) and 10 μL of DMF were slurried in benzene (10 mL). Oxalyl chloride (760 μL, 7.6 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1

hour. The volatiles were evaporated on a rotary evaporator and the residue was reconcentrated from 5 mL of benzene. The reisdue was taken up in methylene chloride (10 mL) and cooled to 0°C. To this solution was added the the product of Example 19a (2.2 g, 7.6 mmol) and pyridine (630 μL, 7.6 mmol) in methylene chloride (14 mL). The reaction was kept cold for 15 minutes then allowed to warm to room temperature. After 1 hour the mixture was diluted with methylene chloride and washed (1 X 10) with 0.3 N HCl and satd $NaHCO_3$. The solvent was dried over Na_2SO_4 and evaporated on a rotary evaporator. ^{1}H-NMR ($CDCl_3$) δ: 7.72 (d, J = 8.5 Hz, 1 H), 7.70 (d, J = 8.6 Hz, 1 H), 7.64 (s, 1 H), 7.37 (dd, J = 1.8 and 8.5 Hz, 1 H), 7.15 (dd, J = 2.5 and 8.9 Hz, 1 H), 7.11 (d, j = 2.5 Hz, 1 H), 6.35 (t, J =, 1 H), 5.05 (d, J = , 1 H), 4.47 (dd, J = 4.6 and 11 Hz, 1 H), 4.10-4.35 (mult, 2H),3.91 (s, 3 H), 3.88 (q, J = 7.2 Hz, 1 H), 3.04 (dd, J = 6.3 ands 13.6 Hz, 1 H), 2.88-2.95 (mult, 1 H), 1.56 (d, J = 7.2 Hz, 3 H), 1.39 (s, 9 H), 1.19 (s, 3 H), 1.17 (s, 3H). Anal calcd for $C_{26}H_{36}N_2O_6S$: C, 61.88; H, 7.19; N, 5.55; S, 6.35. Found: C, 62.14; H, 7.07; N, 5.20; S, 6.02.

21b. 3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) propyl ester hydrochloride

The product of Example 21a (500 mg, 1.0 mmol) and tert-butyl nitrite (150 μL, 1.2 mmol) were dissolved in methylene chloride (8 mL) and stirred at room temperature for 1.5 hour. The solvent was evaporated and the residue was filtered through a plug of silica gel to give 470 mg of nitrosothiol. The amine protecting group was removed by stirring in 3N HCl in EtOAc (6 mL) for 1 hour. The solvent was evaporated to give 330 mg (69 % overall) of the title compound as a green solid. ^{1}H-NMR ($CDCl_3$) δ: 9.00 (t, J = 6.0 Hz, 1 H), 8.5 (br s, 3 H), 7.78 (d, J = 8.9 Hz, 1 H), 7.76 (d, j = 8.5 Hz, 1 H), 7.20 (s, 1 H), 7.39 (dd, J = 1.8 and 8.5 Hz, 1 H), 7.14 (dd, J = 2.5 and 8.9 Hz, 1 H), 4.49 (pent. J = 6.5 Hz, 1 H), 4.14-4.22 (mult, 2 H), 3.87-3.97 (mult , 2 H), 3.85 (s, 3 H), 3.72 (dd, J = 5.6 and 13.9 Hz, 1 H), 1.78/1.80/1.89/1.97 (s, 6 H), 1.45 (d, J = 7.2 Hz, 3H).

Example 22

4-((2-S-Nitroso-2-methyl)-propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

22a. 3-Carboxy-propionic acid-(2-mercapto-2-methyl)-propyl amide

To a solution of succinic anhydride (15 g, 0.15 mol), pyridine (54 g, 0.69 mol), isopropyl alcohol (50 ml), and methylene chloride (150 ml) was added 1-amino-2-methyl-2 propanethiol hydrochloride (23.3 g, 0.16 mol) and the reaction was stirred at room temperature for 4 hours. The reaction was concentrated in vacuo and the residue partioned between ethyl acetate and 1N HCl. The organic phase was dried over sodium sulfate and the volatiles evaporated. The residual oil was recrystalized from ethyl acetate/hexane to afford the product as colorless prisms (22.3g, 73% yield). ^{1}H-NMR ($CDCl_3$) : δ 6.20 (br s, 1 H), 3.35 (d, J = 6.2 Hz, 2 H), 2.74 (m, 2 H), 2.58 (m, 2 H), 1.35 (s, 6H).

22b. 4-Hyroxy-butyric acid-(2-mercapto-2-methyl)-propyl amide

To a solution of the product of Example 22a (1.20 g 5.8 mmol) in anhydrous tetrahydrofuran (10 ml) was added borane dimethylsulfide complex (656 μl, 6.8 mmol) and the reaction mixture was allowed to stand at room temperature for 6 hours. The reaction mixture was concentrated in vacuo and the residue partioned between ethyl acetate and 1N HCl. The organic phase was dried over sodium sulfate to afford the crude product which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 6.16 (br s, 1 H), 3.71 (t, J = 5.7 Hz, 2 H), 3.33 (d, J = 6.2 Hz, 2H) 2.41 (t, J = 6.8 Hz, 2 H), 1.63 (m, 2H) 1.30 (s, 6H).

22c. 4-((2-Mercapto-2-methyl)-propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

The product of Example 7a (0.204 g, 0.82 mmol) was dissolved in anhydrous methylene chloride (2 mL) and pyridine (66 μL, 0.82 mmol) was added. The reaction

mixture was cooled to -78°C and a solution of the product of Example 22b (0.187 g, 0.98 mmol) in anhydrous methylene chloride (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to give 0.190g (59 % yield) of the product as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.53-1.58 (d, 3 H), 1.86-1.95 (m, 2 H), 1.98-2.08 (m, 2 H), 3.15-3.21 (dd, 2 H), 3.80-3.87 (q, 1 H), 3.88 (s, 3 H), 4.02-4.18 (m, 2 H), 5.74 (s, 1 H), 7.07-7.10 (d, 1 H), 7.10-7.15 (dd, 1 H), 7.38-7.43 (dd, 1 H), 7.65 (s, 1 H), 7.65-7.69 (d, 1 H), 7.69-7.72 (d, 1 H).

22d. 4-((2-S-Nitroso-2-methyl)-propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

The product of Example 22c (0.102 g, 0.26 mmol) was dissolved in anhydrous methylene chloride (2 mL) and tert-butyl nitrite (46 μL, 0.39 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature and the solvent was evaporated in vacuo to give 0.105 g (93 % yield) of the title compound as a green oil. ^{1}H NMR ($CDCl_3$) δ 1.53-1.59 (d, 3 H), 1.78 (s, 6 H), 1.81-1.99 (m, 4 H), 3.79-3.86 (q, 1 H), 3.86-3.90 (dd, 2 H), 3.91 (s, 3 H), 3.97-4.18 (m, 2 H), 5.41 (s, 1 H), 7.07-7.10 (d, 1 H), 7.10-7.15 (dd, 1 H), 7.36-7.40 (dd, 1 H), 7.65-7.70 (d, 3 H).

Example 23

2-((2-S-Nitroso-2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

23a. Chloroacetic acid (2-tetrahydropyranyl thioether-2-methyl-propyl)-amide

To a stirred solution of pyridine (2.37 g, 30 mmol), 1-amino-2-methyl-2 propanethiol hydrochloride (2 g, 14 mmol in methylene chloride (30 ml) at 0 °C was added dropwise chloroacetyl chloride (1.7 g, 15 mmol). After the addition was complete and the reaction mixture was stirred overnight with slow warming to room temperature. The reaction was washed with 4N HCl and the organic phase was dried

over sodium sulfate and then concentrated in vacuo. A portion of the residue (0.370g, 2.04 mmol) was combined with dihydropyran (326 μL, 2.24 mmol) and cooled to 0°C. A 4M solution of hydrochloric acid in ethyl ether (14 μL) was added and the reaction mixture was stirred for 3 hours at room temperature. The solvent was evaporated in vacuo to give 0.530 g (98 % yield) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.23-1.42 (d, 6 H), 1.51-1.73 (m, 4 H), 1.74-1.91 (m, 2 H), 3.23-3.35 (dd, 1 H), 3.42-3.58 (m, 2 H), 4.05 (s, 2 H), 4.05-4.11 (dd, 1 H), 4.81-4.89 (dd, 1 H), 7.54 (s, 1 H).

23b. 2-((2-tetrahydropyranyl thioether 2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

Under a nitrogen atmosphere (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid sodium salt (0.514 g, 2.04 mmol) was suspended in anhydrous dimethylformamide (10 mL) and a solution of the product of Example 23a (0.519 g, 2.04 mmol) in anhydrous dimethylformamide (5 mL) was added. The reaction mixture was stirred for 17 hours at room temperature. The solvent was evaporated, the residue was suspended in methylene chloride, and the precipitate was filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to give 0.263 (28 % yield) of the the product as an oil. ^{1}H NMR (CDCl) δ: 1.06-1.15 (d, 3 H), 1.23-1.26 (d, 3 H), 1.43-1.59 (m, 4 H), 1.60-1.66 (d, 3 H), 1.51-1.84 (m, 2 H), 3.04-3.22 (ddd, 1 H), 3.24-3.48 (m, 2 H), 3.87 (s, 3 H), 3.91-4.03 (m, 2 H), 4.41-4.64 (m, 2 H), 4.70-4.76 (m, 1 H), 6.94-7.05 (m, 1 H), 7.06-7.10 (d, 1 H), 7.11-7.15 (dd, 1 H), 7.37-7.46 (dd, 1 H), 7.63-7.71 (m, 3 H).

23c. 2-((2-Mercapto-2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

The product of Example 23b (0.180 g, 0.39 mmol) was dissolved in methanol and a solution of silver nitrate (0.133g, 0.79 mmol) in water (0.5 mL) was added. The reaction mixture was stirred for 30 minutes at room temperature and the solvent

was evaporated. The residue was suspended in dichloromethane (50 mL) and a 4M solution of hydrochloric acid in ethyl ether (1 mL) was added. After 12 hours stirring at room temperature, the precipitate was filtered, the filtrate washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (3:1) to (1:1) to give 0.046 g (31 % yield) of the title compound (2c) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.01-1.11 (d, 6 H), 1.19 (s, 1 H), 1.59-1.64 (d, 3 H), 2.94-3.03 (dd, 1 H), 3.15-3.24 (dd, 1 H), 3.90 (s, 3 H), 3.91-4.00 (q, 1 H), 4.43-4.50 (d, 1 H), 4.70-4.77 (d, 1 H), 6.13 (s, 1 H), 7.07-7.11 (d, 1 H), 7.12-7.17 (dd, 1 H), 7.37-7.44 (dd, 1 H), 7.65-7.74 (m, 3 H).

23d. 2-((2-S-Nitroso-2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

The product of Example 23c (0.040 g, 0.11 mmol) was dissolved in anhydrous methylene chloride (1 mL) and tert-butyl nitrite (19 μL, 0.16 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature and the solvent was evaporated in vacuo to give 0.043 g (100 % yield) of the title compound as a green oil. ^{1}H NMR ($CDCl_3$) δ: 1.54 (s, 3 H), 1.56-1.61 (t, 6 H), 3.59-3.68 (dd, 1 H), 3.92 (s, 3 H), 3.82-3.91 (m, 2 H), 4.02-4.46 (d, 1 H), 4.69-4.75 (d, 1 H), 5.90 (s, 1 H), 7.09-7.12 (d, 1 H), 7.13-7.18 (dd, 1 H), 7.29-7.34 (dd, 1 H), 7.61-7.71 (m, 3 H).

Example 24

3-S-Nitro-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

To a solution of the product of Example 6a (103 mg, 0.29 mmol) in methylene chloride (3 ml) was bubbled in dinitrogen tetroxide till saturation. The reaction mixture was allowed to stand at room temperature for 20 minutes and the the excess dinitrogen tetroxide was blown off by bubbling nitrogen gas through the solution. The volatiles were evaporated and the residue purified by flash silica gel chromatography eluting with ether/hexanes (2:1) to afford 93.7 mg (80 %) of the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 3 H), 1.45 (s, 3 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.69 (br s, 1 H), 2.26 (t, J = 6.4 Hz, 2 H), 3.78 (q, J = 7.0 Hz, 3 H), 4.23 (td, J = 6.35 Hz, J = 2.25 Hz, 2 H), 7.4-7.8 (m, 9H).

Example 25

5-(1, 3-(2-S-Nitroso-2-methyl)-dipropyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) isophthalic ester

25a. 5-Acetoxyisophthalic acid

To a stirred solution of isophthalic acid (2.0 g, 11.0 mmol) in pyridine (10 ml) was added acetic anhydride 1.23 g, 12.1 mmol) and the reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue partioned between ethyl acetate and 2N HCl. The organic phase was dried over sodium sulfate and the volatiles evaporated to afford 2.17 g (88 %) of the product as a white solid. ^{1}H NMR ($CDCl_3$/DMSO) δ:2.33 (s, 3 H), 7.71 (m, 2 H), 8.60 (m, 2 H).

25b. 5-Acetoxy-(1, 3-(2-mercapto-2-methyl)-dipropyl) amide

To a solution of the product of Example 25a (506 mg, 2.26 mmol) in anhydrous tetrahydrofuran (6 ml) was added dimethylformamide (1 drop) and oxalyl chloride (631 mg, 5 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. Concentration of the volatiles in vacuo folloed by azeotroping the residue with additional tetrahydrofuran (2 x 5 ml) afforded the crude acid chloride which was used without further purification in the next step. To a solution of 2-amino-2-methyl-2-propanethiol hydrochloride (720 mg, 5 mmol), pyridine (2.34 g, 29 mmol) in methylene chloride (10 ml) was added the acid chloride in methylene chloride (5 ml) and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated in vacuo and the residue partioned between methylene chloride and 1N HCl-brine. The organic phase was dried over sodium sufate and the volatiles evaporated to afford 693 mg (82 %) the crude product as a white solid. ^{1}H NMR ($CDCl_3$) δ: 1.43

(s, 12 H), 1.71 (s, 2 H), 2.36 (s, 3 H), 3.55 (d, J = 6.2 Hz, 4 H), 6.80 (m, 2 H), 7.27 (s, 2 H), 7.71 (d, J = 1.5 Hz, 1 H).

25c. 5-Hydroxy-1, 3-(2-mercapto-2-methyl)-dipropyl amide

To the product of Example 25b (690 mg, 1.8 mmol) in methanol (10 ml) was added lithium hydroxide monohydrate (90 mg, 2.1 mmol) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue partioned between ethyl acetate and 1N HCl-brine. The organic phase was dried over sodium sulfate and and the volatiles evaporated to afford 540 mg (90 %) of the crude product as a white solid. ^{1}H NMR ($CDCl_3$) δ:1.42 (s, 12 H), 1.71 (s, 2 H), 3.53 (d, J = 6.1 Hz, 4 H), 6.92 (m, 2 H), 7.62 (s, 2 H), 7.74 (s, 1 H).

25d. 5-(1, 3-(2-Mercapto-2-methyl)-dipropyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) isophthalic ester

To a stirred solution of (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (69 mg, 0.30 mmol) in tetrhydrofuran (2 ml) at 0°C was added triethylamine (32 mg, 0.32 mmol) and isobutyl chloroformate (40 mg, 0.30 mmol) and the reaction mixture was stirred for an additional 10 minutes. The product of Example 25c (100 mg, 0.30 mmol) and pyridine (5 ml) were added and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo and the residue purified by flash silica gel chromatography to afford 22 mg (13 %) of the product as a white solid. ^{1}H NMR ($CDCl_3$) δ:1.38 (s, 12 H), 1.52-1.74 (m, 5 H), 3.48 (d, J = 6.1 Hz, 4 H), 3.91 (s, 3 H), 4.12 (q, J = 7.0 Hz, 1 H), 6.73 (m, 2 H), 7.18 (m, 2 H), 7.48 (d, J = 7.2 Hz, 1 H), 7.50 (s, 2 H), 7.58-7.77 (m, 3 H), 8.05 (s, 1 H).

25e. 5-(1, 3-(2-S-Nitroso-2-methyl)-dipropyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) isophthalic ester

The product of Example 25d (0.018 g, 0.032 mmol) was dissolved in anhydrous methylene chloride (1 mL) and cooled to 0°C. Tert-butyl nitrite (20 μL, 0.17 mmol)

was added and the resulting mixture was stirred for 25 minutes. The solvent was evaporated in vacuo to give 0.018 g (90 % yield) of the title compound as a green solid. ^{1}H NMR ($CDCl_3$) δ: 1.66-1.73 (d, 3 H), 1.89 (s, 12 H), 3.93 (s, 3 H), 4.04-4.13 (q, 1 H), 4.15-4.19 (d, 4 H), 6.54-6.58 (t, 2 H), 7.15 (s, 1 H), 7.16-7.19 (d, 1 H), 7.42-7.48 (m, 3 H), 7.70-7.80 (m, 4 H).

Example 26

Comparative *In Vivo* Analgesic, Antiinflammatory and Gastric Lesion Activities

The phenylbenzoquinone-induced writhing test in mice was used to measure analgesic activity. The ability of the compounds to inhibit phenylbenzoquinone-induced writhing in mice was measured using the method of Siegmund *et al., Proc. Soc. Exp. Biol. Med. 95*: 729-731, 1957. Male CD-1 mice (Charles River Laboratories, Wilmington, MA) weighing 20-25 g were fasted overnight. Vehicle or compounds were administered by oral gavage 1 hour prior to i.p. injection of 2 mg/kg of phenylbenzoquinone. In the case of a nitric oxide adduct being given in combination with a NSAID, the nitric oxide adduct was administered immediately before the NSAID. Five minutes after the i.p. injection of phenylbenzoquinone, the number of writhes in a 5 minute period was counted.

The rat paw edema test was used to measure antiinflammatory activity. The rat paw edema test was performed according to the method of Winter *et al., Proc. Soc. Exp. Biol. Med. 111*: 544-547, 1962. Male Sprague-Dawley rats (250-275 g) were fasted overnight and dosed by oral gavage with vehicle or suspensions of compound one hour prior to the subplantar injection of 50 μl of 1% suspension of carrageenin. Three hours later, the paw volume was measured and compared with the initial volume measured immediately after carrageenin injection.

The rat gastric lesion test (Kitagawa *et al., J. Pharmacol. Exp.Ther., 253*:1133-1137, 1990; Al-Ghamdi *et al., J. Int. Med. Res., 19*: 2242, 1991) was used to evaluate the potential of compounds to produce gastric lesion. Male Sprague Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 230-250 g were used for the experiments. The rats were housed with laboratory chow and water *ad libitum* prior to the study. The rats were fasted for 24-30 hours with free access to water and then dosed by oral gavage with vehicle or with drugs given at a volume of 0.5 mL/100 g. For the unmodified NSAIDs being given in combination with a nitric oxide adduct (NO-adduct), the NO-adduct was administered by oral gavage immediately prior to the administration of NSAID by oral gavage. Food was withheld for 18 hours after the inital dosing. For acute studies, rats were euthanized by CO_2 eighteen hours after dosing and the stomachs were dissected. For the multiple dosing studies, the results of which are in Table 3, food was given eighteen hours after the first dose and the rats were maintained on food and water *ad libitum* while receiving a single daily dose for the remainder of the experiment. For the multiple dosing studies, the results of which are in Table 4, the rats were either fasted 24-30 hours before the first dosing and for 4 hours after the first dosing, (4 day study with ketoprofen, Example 4, and Example 6); allowed access to food and water *ad libitum* before as well as during the experiment, (7 day study with ketoprofen and Example 4); or fasted 24-30 hours prior to the first dosing and for 18 hours after the first dosing, (7 day study with ibuprofen, Example 11, and Example 12). The stomachs were dissected along the greater curvature, washed with a directed stream of 0.9% saline and pinned open on a sylgard based petridish for examination of the hemorrhagic lesion. Gastric lesion score was expressed in mm and calculated by summing the length of each lesion.

Table 1 shows the relative activities of compounds in the analgesic, antiinflammatory and gastric lesion tests, and are expressed, for each novel NSAID compound, as described according to the general formulas (I), (II), (III) and (IV), or NSAID coadministered with an NO-adduct, as the ratio of activitiy relative to the parent NSAID.

Table 1

	Relative Activity		
Compound	Analgesia	Antiinflammation	Gastric Lesion
Ketoprofen	1	1	1
Example 4	1.6	0.7	0.03
Example 6	1	ND	ND
Example 5	1.1	ND	ND
Example 16	1.1	ND	ND
Flurbiprofen	1	1	1
Example 13	0.31	1.83	0.5
Indomethacin	1	1	1
Example 8	1	1	0.08
Ibuprofen	ND	1	1
Example 12	ND	1	<0.03
Example 11	ND	1	<0.05
Piroxicam	1	ND	1
Piroxicam + Example 2	1.3	ND	0.08

ND - not determined

Table 2 shows the results of single dose treatment studies in which various NO-adducts were administered in combination with various NSAIDs. The combinations are able to protect against the NSAID induced gastric toxicity.

Table 2

NSAID	(mg/kg)	NO-Adduct	Molar Dose Ratio NSAID : NO-Adduct	Gastric Lesion Protection
Piroxicam	16	Example 2	1 : 1	+++
Piroxicam	8	Example 2	1 : 1	+++
Piroxicam	8	Isoamyl nitrite	1 : 3	+++
Piroxicam	8	Isosorbide dinitrate	1 : 3	+++
Piroxicam	8	Example 1	1 : 2	++
Flurbiprofen	16	Example 2	1 : 1	++
Tenidap	16	Example 2	1 : 1	++
Indomethaacin	20	Example 2	1 : 1	++
Tenidap	22.5	Example 1	1 : 1	+++

70-100% Protection = +++; 40-69% Protection = ++; 20-39% Protection = +

Table 3 shows the results of multiple dose treatment studies in which various NO-adducts were administered in combination with various NSAIDs. The combinations are able to protect against the NSAID induced gastric toxicity.

Table 3

Treatment (Days)	NSAID	(mg/kg)	Molar Dose Ratio NO-Donor	Gastric Lesion NSAID : NO-Adduct	Protection
3	Piroxicam	16	Example 2	1 : 1	+++
14	Piroxicam	16	Example 2	1 : 1	++
7	Ibuprofen	40	Example 2	1 : 1	+
14	Ibuprofen	30	Example 2	1 : 1	++

70-100% Protection = +++; 40-69% Protection = ++; 20-39% Protection = +

Table 4 shows the results of multiple dose treatment studies in which various novel NSAID compounds directly or indirectly linked to various NO-adducts were administered. The modified NSAIDs containing NO-adducts produced significantly less gastric toxcity.

Table 4

Compound	(mg/kg)	Treatment (Days)	Relative Gastric Lesion Activity
Ketoprofen	10	4	+++++
Example 4	14	4	+
Example 6	15	4	++
Ketoprofen	10	7	+++++
Example 4	14	7	+
Ibuprofen	30	7	+++++

Example 11	50	7	+
Example 12	45	7	+
Vehicle		7	+

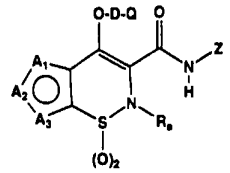
100% of the gastric toxcity induced by the parent NSAID = +++++
21-40% of the gastric toxcity induced by the parent NSAID = ++
1-20% of the gastric toxcity induced by the parent NSAID = +

What Is Claimed Is:

1. A non-steroidal antiinflammatory agent to which is directly or indirectly linked at least one NO group.

2. The non-steroidal antiinflammatory agent of claim 1 which is selected from the group consisting of:

(i) compounds having the structure



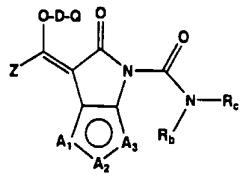
I

wherein

D is selected from (i) a covalent bond; (ii) $-C(R_a)-O-C(O)-Y-[C(R_b)(R_c)]_p-T$ in which R_a is lower alkyl, cycloalkyl, aryl or heteroaryl, Y is oxygen, sulfur, or NR_i in which R_i is hydrogen or lower alkyl, R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, aminoarylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6 and T is a covalent bond, oxygen, sulfur, or nitrogen and Q is -NO or $-NO_2$ with the proviso that -T-Q is not $-O-NO_2$; or (iii) $-(CO)-T_1-[C(R_b)(R_c)]_p-T_2$ wherein T_1 and T_2 are independently selected from T, and wherein R_b, R_c, p and T are as defined above and with the provision that -T-Q does not equal $-O-NO_2$; Z is an aryl or heteroaryl; and A_1, A_2 and A_3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring and each is independently selected from (1) $C-R_f$ wherein R_f at each occurrence is independently selected from hydrogen, lower alkyl, lower haloalkyl, alkoxyalkyl, halogen or nitro; (2) $N-R_g$ wherein R_g at each occurrence is independently selected from a covalent bond to an adjacent ring atom in order to render the ring aromatic, hydrogen, lower alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; (3) sulfur; (4) oxygen; and (5)

$B_a=B_b$ wherein B_a and B_b are each independently selected from nitrogen or C-R_1 wherein at each occurrence R_1 is as defined above;

(ii) compounds having the structure

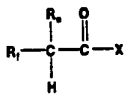


II

wherein

R_b, R_c, D, Q, Z, A_1, A_2 and A_3 are as defined above;

(iii) compounds having the structure

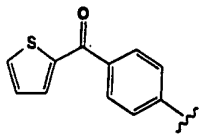


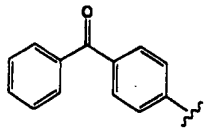
III

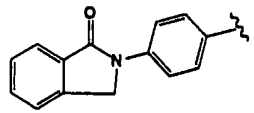
wherein

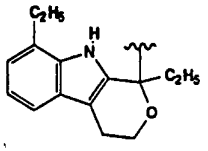
R_e is hydrogen or lower alkyl;

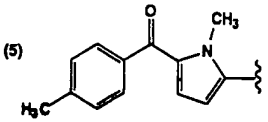
R_f is selected from

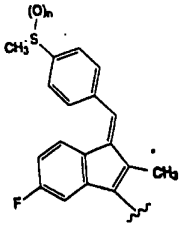
(1) 

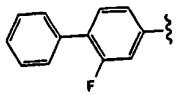
(2) 

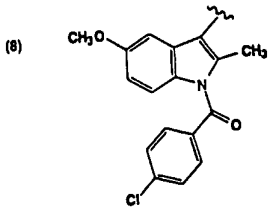
(3) 

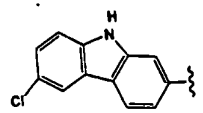
(4) 

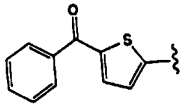
(5) 

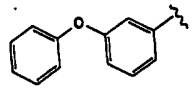
(6) 

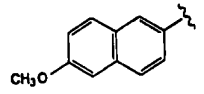
(7) 

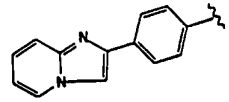
(8) 

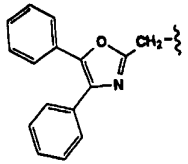
(9) 

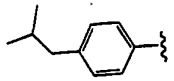
(10) 

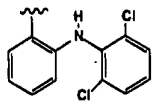
(11) 

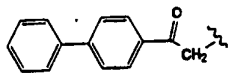
(12) 

(13) 

(14) 

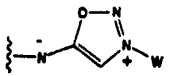
(15) 

(16) 

(17) 

in which n is 0 or 1; and

X is (1) -Y-[C(R_b)(R_c)]p_1-G-[C(R_b)(R_c)]p_2-T-Q, wherein G is (i) a covalent bond; (ii) -T-C(O)-; (iii) -C(O)-T; (iv) -C(Y-C(O)-R_m)- wherein R_m is heteroaryl or heterocyclic ring; p_1 and p_2 are independently selected from p and in which Y, R_b, R_c, p and T are as defined above with the proviso that -T-Q is not -O-NO_2; (2)

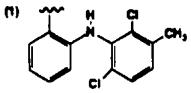


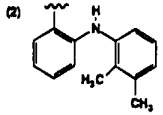
in which W is a heterocyclic ring or NR_hR_i wherein R_h and R_i are independently selected from lower alkyl, aryl or alkenyl; (3) -Y_1[C(R_b)(R_c)]$_s$-Z-[C(O)-Y_2-[C(R_b)(R_c)]$_{P1}$-T-Q]$_{P2}$ wherein Y_1, and Y_2 are independently selected from Y, S is an integer from 0 to 3, and R_b, R_c, Z, T, and Q are as defined above with the proviso that -T-Q is not is -O-NO_2; and compounds having the structure

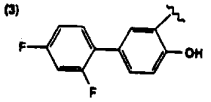
IV

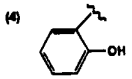
wherein

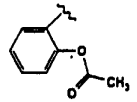
R_g is selected from

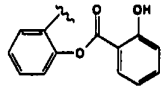
(1) 

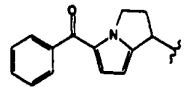
(2) 

(3) 

(4) 

(5) 

(6) 

(7) 

and X is defined as above.

3. A composition comprising (i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug and (ii) an NSAID toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

4. The composition of claim 3 wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of salicylic acid derivatives, pyrazolon derivatives, para-aminophenol derivatives, indole derivatives, fentamates, tolmetin, propionic acid derivatives, oxicam derivatives, phenylacetic acid derivatives, cytokine inhibitors, cyclooxygenase inhibitors and selective cyclooxygenase-1 inhibitors as well as cyclooxygenase-2 inhibitors.

5. The composition of claim 4 wherein the salicylic acid derivatives are selected from the group consisting of acetylsalicylic acid, diflunisal, salsalate, sodium salicylate, salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, mesalamine, sulfasalazine and methylsalicylate; the pyrazolon derivatives are selected from the group consisting of phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone; the para-aminophenol derivatives are selected from the group consisting of phenacetin and acetaminophen; the indole derivatives are selected

from the group consisting of indomethacin and sulindac; the fenamates are selected from the group consisting of mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids and pharmaceutically acceptable salts thereof; the propionic acid derivatives are selected from the group consisting of ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, fenbufen, miroprofen, corprofen, pirprofen, oxaprozin, indoprofen and tiaprofenic acid and pharmaceutically acceptable salts thereof; the oxicam derivatives are selected from the group consisting of piroxicam, isoxicam, amperoxicam tenoxicam and the related compound tenidap; the phenylacetic acid derivative is tolmetin or diclofenac and pharmaceutically acceptable salts thereof; the cyclooxygenase inhibitors are selected from the group consisting of etodolac and nabumetone; the selective cyclooxygenase-2 inhibitors are selected from the group consisting of CGP 28238 (6-(2,4-difluorophenoxy)-5-methyl-sulfonylamino -1-indanone), SC-58125 (1-[(4-methylsulfonyl)phenyl]-3- trifluoromethyl-5-(4-fluorophenyl)pyrazole), NS-398 (N-[2-(cyclohexyloxy)-4-nitro-phenyl]methanesulfonamide), DuP 697 (5-bromo-2(fluorophenyl)-3-(4-methylsulfonylphenyl) thiophene), L-745,337 (5-methanesulphonamida-6-(2,4-difluorthiophenyl)-1-indanone), the 1,2-substituted diarylcyclopentene analogues such as 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; and the quinazolinone, such as proquazone.

6. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

7. The composition of claim 6 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

(i) $CH_3[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20 and R_b and R_c are as defined above;

(ii) $HS[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20; and

(iii) $ONS[C(R_b)(R_c)]_xV$

wherein x equals 2 to 20 and V is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro and aryl; and R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, hereroaryl, arylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl.

8. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is selected from the group consisting of:

(i) compounds that include at least one ON-O-, ON-N- or ON-C- group;

(ii) 2-hydroxy-2-nitrosohydrazine which has an $R_{100}R_{200}$-N(O-M^+)-NO group wherein R_1 and R_2 include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds; and

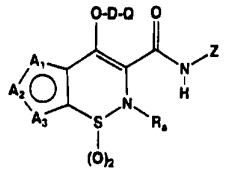
(iii) a thionitrate which has the structure R_{100}-(S)-NO_2 wherein R_{100} includes polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, and a hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon.

9. A composition comprising a non-steroidal antiinflammatory agent to which is directly or indirectly linked at least one NO group and a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

10. The composition of claim 9 wherein the nonsteroidal antiinflammatory drug is a compound which has been nitrosylated through a site selected from the group consisting of oxygen, sulfur, carbon and nitrogen.

11. The composition of claim 9 wherein the nitroso substituted compounds is selected from the group consisting of:

(i) compounds having the structure



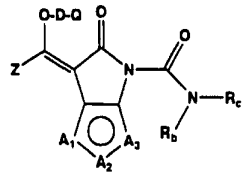
I

wherein

D is selected from (i) a covalent bond; (ii) $-C(R_b)-O-C(O)-Y-[C(R_b)(R_c)]_p-T$ in which R_a is lower alkyl, cycloalkyl, aryl or heteroaryl, Y is oxygen, sulfur, or NR_i in which R_i is hydrogen or lower alkyl, R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, aminoarylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6 and T is a covalent bond, oxygen, sulfur, or nitrogen and Q is -NO or $-NO_2$ with the proviso that -T-Q is not $-O-NO_2$; or (iii)$-(CO)-T_1-[C(R_b)(R_c)]_p-T_2$ wherein T_1 and T_2 are independently selected from T, and wherein R_b, R_c, p and T are as defined above and with the provision that -T-Q does not equal $-O-NO_2$; Z is an aryl or heteroaryl; and A_1, A_2 and A_3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring and each is independently selected from (1) $C-R_i$ wherein R_i at each occurrence is independently selected from hydrogen, lower alkyl, lower haloalkyl, alkoxyalkyl, halogen or nitro; (2) $N-R_d$ wherein R_d at each occurrence is independently selected from a covalent bond to an adjacent ring atom in order to render the ring aromatic, hydrogen,

lower alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; (3) sulfur; (4) oxygen; and (5) $B_a=B_b$ wherein B_a and B_b are each independently selected from nitrogen or $C-R_i$ wherein at each occurrence R_i is as defined above;

(ii) compounds having the structure

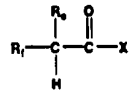


II

wherein

R_b, R_c, D, Q, Z, A_1, A_2 and A_3 are as defined above;

(iii) compounds having the structure

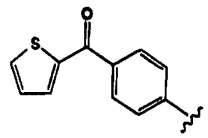


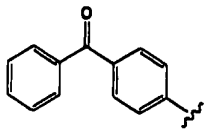
III

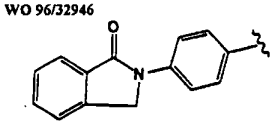
wherein

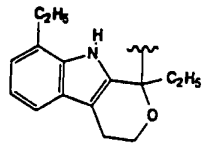
R_c is hydrogen or lower alkyl;

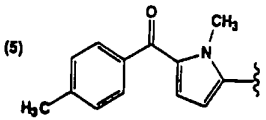
R_f is selected from

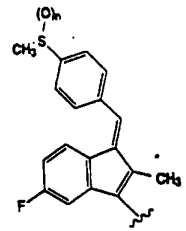
(1) 

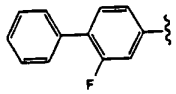
(2) 

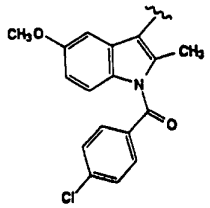
(3) 

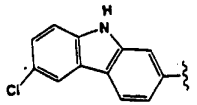
(4) 

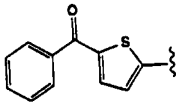
(5) 

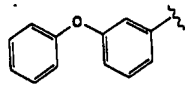
(6) 

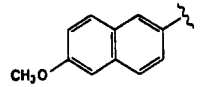
(7) 

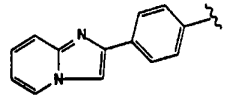
(8) 

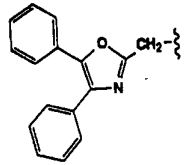
(9) 

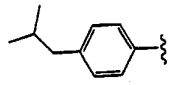
(10) 

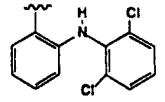
(11) 

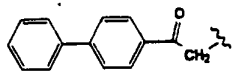
(12) 

(13) 

(14) 

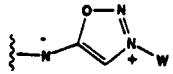
(15) 

(16) 

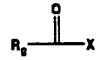
(17) 

in which n is 0 or 1; and

X is (1) -Y-[C(R_b)(R_c)]p_1-G-[C(R_b)(R_c)]p_2-T-Q, wherein G is (i) a covalent bond; (ii) -T-C(O)-; (iii) -C(O)-T; (iv) -C(Y-C(O)-R_m)- wherein R_m is heteroaryl or heterocyclic ring; p_1 and p_2 are independently selected from p and in which Y, R_b, R_c, p and T are as defined above with the proviso that -T-Q is not -O-NO_2; (2)



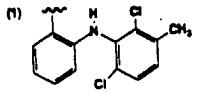
in which W is a heterocyclic ring or NR_hR_i wherein R_h and R_i are independently selected from lower alkyl, aryl or alkenyl; (3) -Y_1[C(R_b)(R_c)]$_s$-Z-[C(O)-Y_2-[C(R_b)(R_c)]$_{P1}$-T-Q]$_{P2}$ wherein Y_1, and Y_2 are independently selected from Y, S is an integer from 0 to 3, and R_b, R_c, Z, T, and Q are as defined above with the proviso that -T-Q is not is -O-NO_2; and compounds having the structure

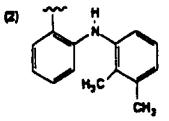


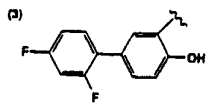
XV

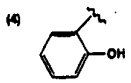
wherein

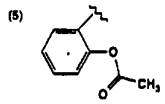
R_g is selected from

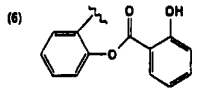
(1) 

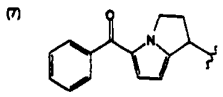
(2) 











and X is defined as above.

12. The composition of claim 9 wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of salicylic acid derivatives, pyrazolon derivatives, para-aminophenol derivatives, indole derivatives, fentamates, tolmetin, propionic acid derivatives, oxicam derivatives, phenylacetic acid derivatives, cytokine inhibitors, cyclooxygenase inhibitors and selective cyclooxygenase-1 inhibitors as well as cyclooxygenase-2 inhibitors.

13. The composition of claim 12 wherein the salicylic acid derivatives are selected from the group consisting of acetylsalicylic acid, diflunisal, salsalate, sodium salicylate, salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, mesalamine, sulfasalazine and methylsalicylate; the pyrazolon derivatives are selected from the group consisting of phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone; the para-aminophenol derivatives are selected from the group consisting of phenacetin and acetaminophen; the indole derivatives are selected from the group consisting of indomethacin and sulindac; the fentamates are selected from the group consisting of mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids and pharmaceutically acceptable salts thereof; the propionic acid derivatives are selected from the group consisting of ibuprofen, naproxen, flurbiprofen,

fenoprofen, ketoprofen, fenbufen, miroprofen, corprofen, pirprofen, oxaprozin, indoprofen and tiaprofenic acid and pharmaceutically acceptable salts thereof; the oxicam derivatives are selected from the group consisting of piroxicam, isoxicam, amperoxicam, tenoxicam, and the related compound tenidap; the phenylacetic acid derivative is selected from the group consisting of tolmetin and diclofenac and pharmaceutically acceptable salts thereof; the cyclooxygenase inhibitors are selected from the group consisting of etodolac and nabumetone; the selective cyclooxygenase-2 inhibitors are selected from the group consisting of CGP 28238 (6-(2,4-difluorophenoxy)-5- methyl-sulfonylamino -1-indanone), SC-58125 (1-[(4-methylsulfonyl)phenyl]-3- trifluoromethyl-5-(4-fluorophenyl)pyrazole), NS-398 (N-[2-(cyclohexyloxy)- 4-nitro-phenyl]methanesulfonamide), DuP 697 (5-bromo-2-(fluorophenyl)-3-(4- methylsulfonylphenyl) thiophene), L-745,337 (5-methanesulphonamida-6-(2,4-diflurorthiophenyl)-1-indanone), the 1,2-substituted diarylcyclopentene analogues such as 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; and a quinazolinone.

14. The composition of claim 9 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

15. The composition of claim 14 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

(i) $CH_3[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20 and R_b and R_c are as defined above;

(ii) $HS[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20; and

(iii) $ONS[C(R_b)(R_c)]_xV$

wherein x equals 2 to 20 and V is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy, alkylsulfinyl, arylthio, alkylamino,

dialkylamino. hydroxy. carbamoyl. N-alkylcarbamoyl, N.N-dialkylcarbamoyl. amino. hydroxyl, carboxyl, hydrogen. nitro and aryl; and x, R_b and R_c are as defined above.

16. The composition of claim 11 wherein the compound that donates. transfers or releases nitric oxide is selected from the group consisting of:

(i) compounds that include at least one ON-O-, ON-N- or ON-C- group;

(ii) 2-hydroxy-2-nitrosohydrazine which has an $R_{100}R_{200}$-N(O-M$^+$)-NO group wherein R_{100} and R_{200} include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds; and

(iii) a thionitrate which has the structure R_{100}-(S)-NO_2 wherein R_{100} includes polypeptides. amino acids. sugars, modified and unmodified oligonucleotides. and a hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon.

17. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of a nonsteroidal antiinflammatory agent of claim 1.

18. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of a nonsteroidal antiinflammatory agent of claim 2.

19. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of the composition of claim 3.

20. A method for treating inflammation, pain. gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of the composition of claim 9.

21. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof which comprises co-administering to said animal a therapeutically effective amount of a nonsteroidal antiinflammatory drug and a nonsteroidal antiinflammatory drug gastrointestinal toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

22. A method of reducing the gastrointestinal toxicity of nonsteroidal antiinflammatory drugs administered to an animal which comprises co-administering to said animal a nonsteroidal antiinflammatory drug gastrointestinal toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

23. A method of reducing the renal toxicity of nonsteroidal antiinflammatory drugs administered to an animal which comprises co-administering to said animal a nonsteroidal antiinflammatory drug renal toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide. or elevates endogenous synthesis levels of nitric oxide.

FIG. 1

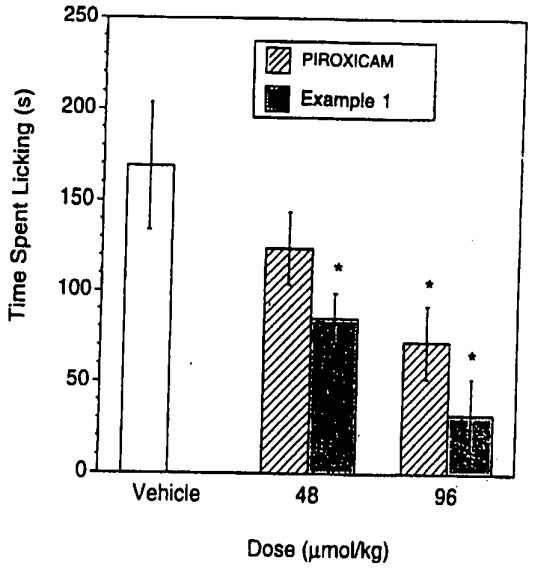
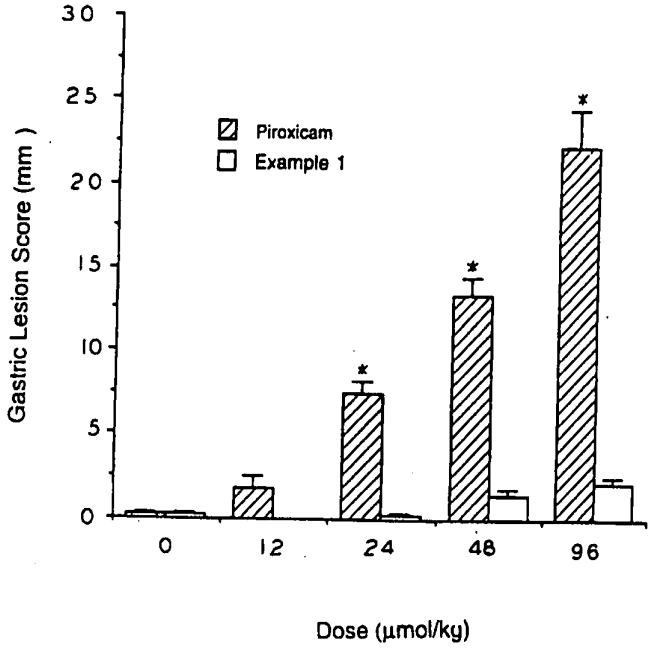

250
200
150
100
50
0
Time Spent Licking (s)
PIROXICAM
Example 1
*
*
*
Vehicle
48
96
Dose (µmol/kg)

FIG. 2


30
25
20
15
10
5
0
Gastric Lesion Score (mm)
Piroxicam
Example 1
*
*
*
*
0
12
24
48
96
Dose (µmol/kg)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/04931

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/54; C07D 513/00, 513/02, 513/04
US CL :544/048, 049; 514/226.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/048, 049; 514/226.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online, Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P --- Y,P	WO, A, 95/30641 (NICOX LIMITED) 16 November 1995, page 23, lines 5-6.	1, 9, 17, 21 --- 1-21
X,P --- Y,P	EP, A1, 0 658,559 (CHEMISCH PHARMAZEUTISCHE FORSCHUNGS-GESELLSCHAFT m.b.H.) 21 JUNE 1995, see entire document.	1, 9, 17, 21 --- 1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 MAY 1996	12 JUL 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer C Tsang for MATTHEW V. GRUMBLING Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/04931

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-21 (part) corresponding to group I.

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula I.

Group II, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula II, in which A1, A2, and A3 form a 6 membered ring containing 4 heteroatoms.

Group III, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula II, in which A1, A2,and A3 form a 6 membered ring containing 3 heteroatoms as set forth.

Group IV, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound (in the compound claims) is of the formula II, in which A1, A2, and A3 form a 6 membered ring containing 2 heteroatoms.

Group V, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula II, in which A1, A2, and A3 form a 6 membered ring containing 1 heteroatom.

Group VI, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound (in the compound claims) is of the formula II, in which A1, A2, and A3 form a 5 or 6 membered ring containing no heteroatom.

Group VII, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the compound (in the compound claims) is of the formula II, in which A1, A2, and A3 form a 5 membered ring containing 3 heteroatoms of which at least one is nitrogen.

Group VIII, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the compound (in the compound claims) is of the formula II, in which A1, A2, and A3 form a 5 membered ring containing 2, of which at least one is nitrogen.

Group IX, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the compound (in the compound claims) is of the formula II, in which A1, A2, and A3 form a 5 membered ring containing 1 nitrogen, as the only hetero ring atom.

Group X, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound (in the compound claims) is of the formula II, in which A1, A2, and A3 form a 5 membered ring containing one to three non-nitrogen ring atoms as the only hetero ring atom(s).

Group XI, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound (in the compound claims) is of the formula III, in which Rf is of subformula 1 or 10.

Group XII, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula III, in which Rf is of subformulae 2, 6, 7, 11, 12, 15, 16 or 17 or of formula IV in which Rf is one of subformulae 1, 2, 3, 4, 5 or 6.

Group XIII, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula III, in which Rf is of subformulae 3 or 8 or of formula IV in which R is subformula 7.

Group XIV, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula III, in which Rf is one of subformulae 4 or 9.

Group XV, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compoundisof the formula III, in which Rf is of subformula 5.

Group XVI, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the

subject compound is of the formula III, in which Rf is subformula 13.

Group XVII, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the subject compound is of the formula III, in which Rf is of subformula 14.

Group XVIII, claim(s) 1-21, drawn to compounds, compositions and methods of anti-inflammatory use in which the compounds are not included in any of the above groups I-XVII.

Group XIX, claim(s) 17-21, drawn to methods of treating pain.

Group XX, claim(s) 17-21, drawn to methods of treating gastrointestinal lesions.

Group XXI, claim(s) 17-21, drawn to methods of treating fever.

Group XXII, claim(s) 22, drawn to methods of treating gastrointestinal toxicity.

Group XXIII, claim(s) 23, drawn to methods of treating renal toxicity.
The inventions listed as Groups I-XXIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

1) Group I-XVIII are distinct from groups XIX-XXIII, which are in turn distinct from each other, because they represent distinct methods of use. One of ordinary skill in the art would not consider one of the methods I-XXIII to be obvious in view of a reference anticipating or rendering obvious one of the other methods. Inflammation, pain, gastrointestinal lesions, renal toxicity and gastrointestinal toxicity are not so similar that treatment of one would necessarily imply or suggest treatment of one the other conditions.

2) Groups I-XVIII are distinct each from the other because they represent distinct structures. A reference that anticipates or renders obvious one of the compounds or compositions of one of the groups I-XVIII would not suggest or render obvious one of the compounds or compositions of one or more other of groups I-XVIII. This is so because they are so structurally dissimilar, differing one from the other in number of heterocyclic rings, number and type of hetero atoms in each hetero ring, number of rings infused cyclic structures (where applicable), size of heterocyclic ring(s), aromaticity, unsaturation and/or saturation of the ring(s), and other factors that would be expected to materially affect the activity of the resulting compounds and compositions.